CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: 063066 /S011, 010, 009, 008, 007, 006

Trade Name : MINOCYCLINE CAPSULES USP 50MG

Generic Name: Minocycline Capsules USP 50mg

Sponsor : Warner Chilcott, Inc.

Approval Date: May 12, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 063066 /S011, 010, 009, 008, 007, 006

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 003066 /S011, 010, 009, 008, 007, 006

APPROVAL LETTERS

AADA 63-066/S-011

Warner Chilcott, Inc.
Division of Warner-Lambert Company
Attention: Norma Enders, R.Ph.
Rockaway 80 Corporate Center
100 Enterprise Dr., Suite 280
Rockaway, NJ 07866

MAY 12

Dear Madam:

This is in reference to your supplemental antibiotic drug application dated April 21, 1997, submitted pursuant to 21 CFR 314.70(c)(Special Supplement - Changes Being Effected) regarding your antibiotic application for Minocycline Hydrochloride Capsules USP, 50 mg.

The supplemental application provides for container labels (50 mg - 20s) reflecting the option to use the proprietary name Vectrin® for your unit-of-use special contract package size.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved antibiotic drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

for 5-12-97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 4/28/97

FROM: John Grace , Consumer Safety Officer

SUBJECT: Special Supplement - Changes Placed into Effect

TO: Document Room

Please make the following entry in the MIS concerning the status of this Special Supplement - Changes Placed into Effect.

ANDA(s)	SUPPLEMENTS(s)	APPL	GRANTED	DENIED
63-066	SLS11			

This form is to accompany the action package/jacket.

Thank you,

4/30/97

Signature of CSO and Date

cc:

ANDA
DIVISION FILE

AADA 63-066/S-010 (50 mg) orange opaque
63-067/S-010 (100 mg) blue opaque

Warner Chilcott, Inc.
Division of Warner-Lambert Company
Attention: Norma Enders, R.Ph.
Rockway 80 Corporate Center
100 Enterprise Dr., Suite 280
Rockaway, NJ 07866

APR 14

Dear Madam:

This is in reference to your supplemental antibiotic drug applications dated November 27, 1996, submitted pursuant to 21 CFR 314.70 regarding your antibiotic applications for Minocycline Hydrochloride Capsules, USP.

Reference is also made to your January 8, 1997 amendments.

The supplemental applications provide for container labels ([50 mg - 100s and 1000s] and [100 mg - 50s and 1000s]) and package insert labeling reflecting additional capsule colors and proprietary name in the following manner:

1. DESCRIPTION - Deletion of specific dye components to create a second capsule color for each strength. were deleted from both the 50 mg and 100 mg capsules strength. and were deleted from the 50 mg capsule strength. The second capsule colors are orange for the 50 mg and blue for the 100 mg strengths.

2. The second capsule color container labels and insert labeling for each strength as well as the 100 mg package of 20s (unit of use) for special contracts will bear the proprietary name "Vectrin®".

3. HOW SUPPLIED - Revised product description, color, imprint, and NDC numbers reflecting the second capsule colors.

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved antibiotic drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

for/ 4-11-97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: AADA 63-066/S-010
63-067/S-010
Dup/Division File 4/2/97
HFD-610/JPhillips
HFD-613/APayne/AVezza/JGrace (no cc:) 4/11/97
HFD-643/RAdams/JHarrison
HFD-600/RF
HFD-82 4/2/97
njg/4/02/97/X:\NEW\FIRMSNZ\WARNCHIL\LTRS&REV\63066S10.APL
Approval letter - Multiple Supplements

AADA 63-066/S-009 (50 mg)
AADA 63-067/S-009 (100 mg)

Warner Chilcott,
Division of Warner-Lambert Company
Attention: Sean Brennan
182 Tabor Road
Morris Plains, NJ 07950

APR 24 1996

Dear Sir:

This is in reference to your supplemental antibiotic drug applications dated March 20, 1996, submitted pursuant to 21 CFR 314.70 (c)(Special Supplement - Changes Being Effected) regarding your antibiotic applications for Minocycline Hydrochloride Capsules USP.

The supplemental applications provide for revised package insert labeling reflecting changes in the CLINICAL PHARMACOLOGY, PRECAUTIONS, and ADVERSE REACTIONS sections.

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for an approved antibiotic drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

4/24/96

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

AADA: 63-066//S-006, 007, 008 (50 mg)
63-067/S-006, 007, 008 (100 mg)

Warner Chilcott, Inc.
Attention: Norma Enders
182 Tabor Road
Morris Plains, NJ 07950

JUN 24 1996

Dear Madam:

This is in reference to your supplemental antibiotic drug applications received March 1, 1996, submitted pursuant to 21 CFR 314.70, regarding your abbreviated antibiotic applications for Minocycline Hydrochloride Capsules, USP.

The supplemental applications provide for:

1. S-006: Elimination of the excess of active drug substance in the formulation.

2. S-007: Addition of batch sizes to and the for minocycline hydrochloride and before the

3. S-008: Stability data for the revised formulation supporting the expiration date of 24 months

We have completed the review of these supplemental applications and they are approved.

We remind you that you must comply with the requirements for approved abbreviated antibiotic applications described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

6/21/96

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

WARNER CHILCOTT
LABORATORIES

Norma A. Enders, R.Ph.
Senior Director,
Regulatory Affairs

FPV

Mr. Douglas Sporn
Director, Office of Generic Drugs
Food and Drug Administration (CDER)
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**Special Supplement-
Changes Being Effected**

APR 21 1997

NDA NO. 63066 REF. NO. S-011

NDA SUPPL FOR LABELING REVISION
S-011 AI

Re: **AADA #63-066**
Minocycline Hydrochloride Capsules USP, 50 mg
Submission of Final Printed Labeling for Bottles of 20 Capsules

Dear Mr. Sporn;

Reference is made to our approved abbreviated antibiotic drug application for Minocycline Hydrochloride Capsules USP, 50 mg. Reference is also made to our labeling supplement S-010, which was approved on April 14, 1997 and permitted the addition of a proprietary name (Vectrin®) for use with a second capsule color of our product.

This "Special Supplement-Changes Being Effected" provides container labels reflecting the Vectrin name for use with one of our approved package sizes (bottles of 20 capsules). For reference, please note that the bottles of 20 capsules were originally approved as part of our initial AADA approval and were supported by completed stability studies. In pre-approval correspondence dated February 22, 1989, it was stated that the bottles of 20 capsules would be available for "Unit of Use" special contracts. We wish to have the option of using the unit of use bottles for our Vectrin product; however, since this package size would not normally be commercially available, in accordance with 21 CFR 201.57(k)(2), we have not modified our insert to include the 20s package size.

Twelve final printed copies of our container labels for bottles of 20 capsules are provided in Attachment A and are arranged as follows: six copies are provided in the archive copy and six copies are provided in the review copy of this submission.

We trust that the enclosed labeling is satisfactory.

RECEIVED
APR 22 1997
GENERIC DRUGS

Sincerely,

Norma A. Enders

Norma A. Enders, R.Ph.
Sr. Director, Regulatory Affairs

Marked 4/25/97

Rockaway 80 Corporate Center • 100 Enterprise Drive • Suite 280 • Rockaway, NJ 07866 • 201-442-3233 • Fax: 201-442-3280

WARNER CHILCOTT
LABORATORIES

Norma A. Enders, R.Ph.
Senior Director,
Regulatory Affairs

January 8, 1997

Mr. Douglas Sporn
Director, Office of Generic Drugs
Food and Drug Administration (CDER)
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

SUPPL AMENDMENT
SL-010/AL

Re: **AADA #63-066**
Minocycline Hydrochloride Capsules USP, 50 mg
Amendment to 11/27/96 Labeling Supplement Proposing the Addition of a Proprietary Name
Submission of Final Printed Labeling

Dear Mr. Sporn;

Reference is made to our approved abbreviated antibiotic drug application for Minocycline Hydrochloride Capsules USP, 50 mg, and to our supplemental application submitted on November 27, 1996, which provided labeling reflecting the addition of a proprietary name (Vectrin®) for our product.

Our pending labeling supplement had provided *draft* container labels and insert labeling for the Agency's review. However, we recognize that *only final printed labeling will be approved by the Office of Generic Drugs*. Since we wish to implement the Vectrin labeling by February 28, 1997, we are now amending the aforementioned supplement with final printed labeling.

Twelve final printed copies of our container labels for bottles of 100 capsules and 1000 capsules are provided in Attachments A and B, respectively. Twelve final printed package inserts are provided in Attachment C. The twelve copies of each labeling piece are arranged as follows: six copies are provided in the archive copy and six copies are provided in the review copy of this submission. Please note that this labeling is identical in text to the draft labeling that was previously submitted. We refer you to our November 27, 1996 submission for a complete discussion regarding the differences between the Vectrin labeling and our currently approved labeling.

If you should have any questions regarding this supplement, or require any additional information, please feel free to contact me at (201) 442-3233.

Sincerely,

RECEIVED
JAN 10 1997
GENERIC DRUGS

Norma A. Enders, R.Ph.
Sr. Director, Regulatory Affairs

Rockaway 80 Corporate Center • 100 Enterprise Drive • Suite 280 • Rockaway, NJ 07866 • 201-442-3233 • Fax: 201-44

WARNER CHILCOTT
LABORATORIES

Norma A. Enders, R.Ph.
Senior Director,
Regulatory Affairs

Mr. Douglas Sporn
Director, Office of Generic Drugs
Food and Drug Administration (CDER)
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

November 27, 1996

NDA NO.
NDA SUPPL #

Re: AADA #63-066
Minocycline Hydrochloride Capsules USP, 50 mg
Labeling Supplement: Addition of a Proprietary Name

Dear Mr. Sporn;

Reference is made to our approved antibiotic drug application for Minocycline Hydrochloride Capsules, USP, 50 mg. Reference is also made to the Office of Generic Drugs' Policy and Procedure Guide #20-90 (as amended on 6/7/95), entitled "Variations in Solid Oral Dosage Forms and Injectables that can be Included within a Single ANDA."

The above-referenced policy guide permits multiple colors of a single shape for a single strength of a solid oral dosage form to be included in the same abbreviated antibiotic drug application. It is our intention to add a second capsule color to this AADA. The second capsule color will be marketed with a proprietary name (Vectrin®) and our originally approved capsule color will continue to be marketed under the generic name. Please note that this new color was obtained via the deletion of specific dye components from our currently approved product. In accordance with 21 CFR 314.70(d)(4), this change does not require prior FDA approval and will be reported in the next annual report. This submission strategy was confirmed via telephone conversation between myself and Mr. P. Rickman of your staff on October 31, 1996.

The purpose of this supplemental application is to provide the Office of Generic Drugs with the opportunity to review and approve labeling that bears the Vectrin brand name. In an October 31, 1996 telephone conversation with Mr. John Grace, also of your staff, I was instructed that this supplement should be submitted for prior approval. *While we believe that the regulations permit this change to be reported in the annual report (in accordance with 21 CFR 314.70(d)(2)), we wish to fully comply with Mr. Grace's recommendations. However, please note that we desire to implement this new labeling by February 28, 1997; therefore, we would appreciate any efforts that your staff can make in providing an expeditious review.*

Rockaway 80 Corporate Center • 100 Enterprise Drive • Suite 280 • Rockaway, NJ 07866 • 201-442-3233 • Fax: 201-442-3280

Four copies of each of our draft labels and package insert labeling are provided in Attachments A through C. Please note that the attached labeling is identical to our currently approved labeling with the following modifications:

1) Addition of the Vectrin brand name and revised NDC numbers that are unique for the Vectrin product.

2) Revision of our company name and address to reflect the sale of Warner Chilcott by the Warner-Lambert Company and the subsequent relocation of our offices. (These actions were previously communicated to the AADA file in correspondence dated March 28, 1996 and November 21, 1996.)

3) In addition to the above items, the package insert bears revisions in the "Description" section (removal of dye components from the inactive ingredients listing) and in the "How Supplied" section (revised product description, color, imprint,etc.).

Finally, we would like to point out that the Vectrin trade name was in use many years ago by Parke-Davis, Division of Warner-Lambert Company, when they distributed minocycline hydrochloride capsules under a licensing agreement with Lederle Laboratories. Warner Chilcott, Inc. has obtained the exclusive rights to the use of the Vectrin trademark. Since the Vectrin name was previously used for this same product, we were hoping that any review conducted by FDA's naming committee, if needed at all, could be handled in an expedited manner.

If you should have any questions regarding this supplement, or require any additional information, please feel free to contact me at (201) 442-3233.

Sincerely,

Norma A. Enders, R.Ph.
Sr. Director, Regulatory Affairs

WARNER CHILCOTT
LABORATORIES
Division of Warner-Lambert Company

Sean Brennan, Ph.D.
Senior Director
Regulatory Affairs

Special Supplement -
Changes Being Effected

Douglas Sporn
Director, Office of Generic Drugs
Food and Drug Administration (CDER)
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAR 20 1996

FPL

NDA NO
NDA SUPPL NO REF NO SL 009
Labeling Rev
SL-009 AI

Re: AADA #63-066
Minocycline Hydrochloride Capsules USP, 50 mg
Labeling Supplement

Dear Mr. Sporn:

This is in response to your letter dated February 5, 1996 in which you commented on the labeling for our abbreviated antibiotic drug applications for Minocycline Hydrochloride Capsules USP, 50 mg and 100 mg.

In your letter, you requested that we revise our package insert labeling for the subject product in accordance with the approved labeling of Minocin® (Lederle Laboratories Division, revised December 1993; approved August 8, 1995).

We have completed these revisions and are submitting twelve copies of our final printed insert labeling in Attachment A for your review.

We trust that the enclosed labeling is satisfactory. We are concurrently submitting a similar supplement to our 100 mg strength application (AADA #63-067). If you should require any additional information, please do not hesitate to contact me at (201) 540-7181, or Norma Enders of my staff at (201) 540-4333.

Sincerely,

Norma Enders for

Sean Brennan, Ph. D.
Senior Director
Regulatory Affairs

3-26-96

182 Tabor Road • Morris Plains, New Jersey 07950 • (201) 540-7181 • Fax: (201) 631-7769

NDA NO. _____ REF. NO. 50066

NDA SUPPL FOR Formulation Change

RECEIVED

MAR 04 1996

BIOAVAILABILITY

GENERIC DRUGS

WARNER CHILCOTT
LABORATORIES
Division of Warner-Lambert Company

Sean Brennan, Ph.D.
Senior Director
Regulatory Affairs

NDA NO. _____ REF. NO. 50066

NDA SUPPL FOR [redacted]

MAR 01 1996

RECEIVED

FEB 07 1996

GENERIC DRUGS

Charles Ganley, MD
Acting Director, Office of Generic Drugs
Food and Drug Administration (CDER)
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA NO. _____ REF. NO. 50066

NDA SUPPL FOR [redacted]

Re: AADA #63-066
Minocycline Hydrochloride Capsules USP, 50 mg
Supplement: Removal of the Excess of Minocycline Hydrochloride USP, in the Formulation and Increase of the Maximum Allowable Batch Size

Dear Dr. Ganley;

Reference is made to our currently approved abbreviated antibiotic drug application for Minocycline Hydrochloride Capsules USP, 50 mg, which is manufactured at our facility in Lititz, Pennsylvania. At this time we would like to supplement our approved application to provide for a reformulation of the product to remove the excess of active drug substance, Minocycline Hydrochloride, USP. We would also like to incorporate a increase in our maximum batch size for this product. Information to support these changes are provided in Attachments 1 through 7, as indicated. Our 100 mg capsule product is covered by a separate AADA (63-067), which is concurrently being supplemented for these changes.

Our currently approved formulation includes a excess of Minocycline Hydrochloride, USP. We desire to change our formulation for Minocycline Hydrochloride Capsules USP, for the 50 mg and 100 mg strength capsule products by removing this excess, and making an appropriate adjustment in the amount of to maintain the target capsule weight.

In accordance with this proposed formulation change, we have revised our composition page and our Master Formula to reflect the deletion of the excess of drug substance and our desired batch size of These revised AADA pages are contained in Attachments 1 and 2, respectively. Other changes are being proposed in the revised Master Formula. Many of these changes are editorial in nature; however, some enhancements have also been incorporated. For the convenience of the reviewer, we have summarized these changes immediately prior to the proposed master formula appearing in Attachment 2.

In support of this supplement, we have manufactured a batch of Minocycline Hydrochloride Capsules USP, 50 mg, without the excess of Minocycline Hydrochloride, USP. Our executed batch record (including complete packaging records) for lot 976N2L is included in Attachment 3. Warner Chilcott's Certificate of Analysis for this lot is provided in Attachment 4.

AADA 63-066
Dr. Charles Ganley
Minocycline Hydrochloride Capsules, USP

Provided in Attachment 5 is Warner Chilcott's Certificate of Analysis for a reference lot of Minocycline Hydrochloride Capsules USP, 50 mg (lot 13013L). This lot is a routine production batch which was manufactured in accordance with our approved AADA; therefore, it contains ? excess of Minocycline Hydrochloride, USP.

Reference is made to the telephone conversation between Dr. S. Dighe, formerly of the Division of Bioequivalence, and Mr. V. Kumar, Warner Chilcott's former Director of Research and Development, on December 11, 1992 (as cited in a letter dated January 28, 1993). During this conversation, it was agreed that Warner Chilcott would conduct a bioequivalence study to support the removal of the excess from our current formula. We are submitting the final report of this bioequivalence study in our concurrent supplement to our 100 mg strength application (AADA 63-067). This single-dose, two-way crossover study compares the relative bioavailability of Warner Chilcott Minocycline HCl Capsules USP, 100 mg with and without ? overage of Minocycline Hydrochloride, USP taken under fasting conditions (protocol #0801-5011).

Based on the results of this study and comparable formulations, we are requesting waiver of the requirement for an *in vivo* bioequivalence study for our 50 mg strength product, as permitted under 21 CFR 320.22 (d)(2). In support of this request we are including comparative dissolution data for 50 mg and 100 mg strength Warner Chilcott Minocycline Hydrochloride Capsules, USP with and without excess of Minocycline Hydrochloride, USP, in Attachment 6.

Finally, we have included stability data for the reformulated product stored at 40°C/75% RH for 3 months and up to 24 months at 30°C packaged in our currently marketed package sizes (bottles of 50 and 1000 capsules) in Attachment 7. Based on the attached stability data, we are requesting an expiration dating period of 24 months for the reformulated product, which is the same as for our current formulation.

We trust that the enclosed information is satisfactory. In accordance with submission requirements, a field copy of this supplemental application is being concurrently submitted to our home district office in Newark, NJ. If you should require additional information, please do not hesitate to contact me at (201) 540-7181, or Norma Enders of my staff at (201) 540-4333.

Sincerely,

Norma Enders for

Sean Brennan, Ph. D.
Senior Director
Regulatory Affairs

c: Ms. R. Brown (Field Copy)

NDA NO. _____ REF. NO. SC-006 NDA NO. _____ REF. NO. _____

NDA SUPPL FOR Manufacturing Revision NDA SUPPL FOR Formulation Revision

NDA NO. _____ REF NO. SC-008

NDA SUPPL FOR Expiration Date

WARNER CHILCOTT
LABORATORIES
Division of Warner-Lambert Company

Sean Brennan, Ph.D.
Senior Director
Regulatory Affairs

RECEIVED
MAR 01 1996

Charles Ganley, MD
Acting Director, Office of Generic Drugs
Food and Drug Administration (CDER)
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAR 04 1996

GENERIC DRUGS

RECEIVED
~~FEB 07 1996~~

GENERIC DRUGS

Re: AADA 63-067
Minocycline Hydrochloride Capsules USP, 100 mg
Supplement: Removal of the Excess of Minocycline Hydrochloride USP, in the Formulation and Increase of the Maximum Allowable Batch Size

Dear Dr. Ganley;

Reference is made to our currently approved abbreviated antibiotic drug application for Minocycline Hydrochloride Capsules USP, 100 mg, which is manufactured at our facility in Lititz, Pennsylvania. At this time we would like to supplement our approved application to provide for a reformulation of the product to remove the excess of active drug substance, Minocycline Hydrochloride, USP. We would also like to incorporate increase in our maximum batch size for this product. Information to support these changes are provided in Attachments 1 through 7, as indicated. Our 50 mg capsule product is covered by a separate AADA (63-066), which is concurrently being supplemented for these changes.

Our currently approved formulation includes a excess of Minocycline Hydrochloride, USP. We desire to change our formulation for Minocycline Hydrochloride Capsules USP, for the 50 mg and 100 mg strength capsule products by removing this excess, and making an appropriate adjustment in the amount of to maintain the target capsule weight.

In accordance with this proposed formulation change, we have revised our composition page and our Master Formula to reflect the deletion of the excess of drug substance and our desired batch size of These revised AADA pages are contained in Attachments 1 and 2, respectively. Other changes are being proposed in the revised Master Formula. Many of these changes are editorial in nature; however, some enhancements have also been incorporated. For the convenience of the reviewer, we have summarized these changes immediately prior to the proposed master formula appearing in Attachment 2.

In support of this supplement, we have manufactured a batch of Minocycline Hydrochloride Capsules USP, 100 mg, without the excess of Minocycline Hydrochloride, USP. Our executed batch record (including complete packaging records) for lot 977N2L is included in Attachment 3. Warner Chilcott's Certificate of Analysis for this lot is provided in Attachment 4.

AADA 63-067
Dr. Charles Ganley
Minocycline Hydrochloride Capsules, USP

Provided in Attachment 5 is Warner Chilcott's Certificate of Analysis for a reference lot of Minocycline Hydrochloride Capsules USP, 100 mg (lot 637D2L). This lot is a routine production batch which was manufactured in accordance with our approved AADA; therefore, it contains ? excess of Minocycline Hydrochloride, USP. This lot served as the reference formulation for a single-dose bioequivalence study, which is discussed below.

Reference is made to the telephone conversation between Dr. S. Dighe, formerly of the Division of Bioequivalence, and Mr. V. Kumar, Warner Chilcott's former Director of Research and Development, on December 11, 1992 (as cited in a letter dated January 28, 1993). During this conversation, it was agreed that Warner Chilcott would conduct a bioequivalence study to support the removal of the excess from our current formula. We are submitting the final report of this bioequivalence study in Attachment 6. This single-dose, two-way crossover study compares the relative bioavailability of Warner Chilcott Minocycline HCl Capsules USP, 100 mg with and without ? overage of Minocycline Hydrochloride, USP taken under fasting conditions (protocol #0801-5011).

Included in the final report for the above-mentioned bioequivalence study are the summary tables of the *in vivo* bioequivalence study, and comparative dissolution profiles for batches of both the 50 mg and 100 mg strength products, with and without the excess of Minocycline Hydrochloride, USP. Also included with the bioequivalence study is the analytical method used in this study for the determination of minocycline levels in human plasma and the validation data for the assay methodology.

In addition, we are submitting a computer diskette containing the raw data collected for this study. A hard copy of these data is provided in both review and archival copies of this application. A copy of the case report forms is also included in this submission as a separately bound volume.

Based on the results of this study and comparable formulations, our concurrent supplement for our 50 mg strength application (AADA 63-066) contains a request for a waiver of the requirement for an *in vivo* bioequivalence study, as permitted under 21 CFR 320.22 (d)(2). In support of this request we are including comparative dissolution data for 50 mg and 100 mg strength Warner Chilcott Minocycline Hydrochloride Capsules, USP with and without cess of Minocycline Hydrochloride, USP.

Finally, we have included stability data for the reformulated product stored at 40°C/75% RH for 3 months and up to 24 months at 30°C packaged in our currently marketed package sizes (bottles of 50 and 1000 capsules) in Attachment 7. Based on the attached stability data, we are requesting an expiration dating period of 24 months for the reformulated product, which is the same as for our current formulation.

AADA 63-067
Dr. Charles Ganley
Minocycline Hydrochloride Capsules, USP

We trust that the enclosed information is satisfactory. In accordance with submission requirements, a field copy of this supplemental application is being concurrently submitted to our home district office in Newark, NJ. If you should require additional information, please do not hesitate to contact me at (201) 540-7181, or Norma Enders of my staff at (201) 540-4333.

Sincerely,

Norma Enders for

Sean Brennan, Ph. D.
Senior Director
Regulatory Affairs

c: Ms. R. Brown (Field Copy)

WARNER CHILCOTT
LABORATORIES

Norma A. Enders, R.Ph.
Senior Director,
Regulatory Affairs

Mr. Douglas Sporn
Director, Office of Generic Drugs
Food and Drug Administration (CDER)
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

January 8, 1997

SUPPL AMENDEMENT

Re: **AADA #63-067**
Minocycline Hydrochloride Capsules USP, 100 mg
Amendment to 11/27/96 Labeling Supplement Proposing the Addition of a Proprietary Name
Submission of Final Printed Labeling

Dear Mr. Sporn;

Reference is made to our approved abbreviated antibiotic drug application for Minocycline Hydrochloride Capsules USP, 100 mg, and to our supplemental application submitted on November 27, 1996, which provided labeling reflecting the addition of a proprietary name (Vectrin®) for our product.

Our pending labeling supplement had provided *draft* container labels and insert labeling for the Agency's review. However, we recognize that *only final printed labeling will be approved by the Office of Generic Drugs*. Since we wish to implement the Vectrin labeling by February 28, 1997, we are now amending the aforementioned supplement with final printed labeling.

Twelve final printed copies of our container labels for bottles of 20 capsules, 50 capsules, and 1000 capsules are provided in Attachments A, B, and C, respectively. Twelve final printed package inserts are provided in Attachment D. The twelve copies of each labeling piece are arranged as follows: six copies are provided in the archive copy and six copies are provided in the review copy of this submission. Please note that this labeling is identical in text to the draft labeling that was previously submitted. We refer you to our November 27, 1996 submission for a complete discussion regarding the differences between the Vectrin labeling and our currently approved labeling.

If you should have any questions regarding this supplement, or require any additional information, please feel free to contact me at (201) 442-3233.

Sincerely,

RECEIVED
JAN 10 1997
GENERIC DRUGS

Norma Enders, R.Ph.
Sr. Director, Regulatory Affairs

WARNER CHILCOTT
LABORATORIES

Norma A. Enders, R.Ph.
Senior Director,
Regulatory Affairs

Mr. Douglas Sporn
Director, Office of Generic Drugs
Food and Drug Administration (CDER)
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

November 27, 1996

SL010

Re: AADA #63-067
Minocycline Hydrochloride Capsules USP, 100 mg
Labeling Supplement: Addition of a Proprietary Name

Dear Mr. Sporn;

Reference is made to our approved antibiotic drug application for Minocycline Hydrochloride Capsules, USP, 100 mg. Reference is also made to the Office of Generic Drugs' Policy and Procedure Guide #20-90 (as amended on 6/7/95), entitled "Variations in Solid Oral Dosage Forms and Injectables that can be Included within a Single ANDA."

The above-referenced policy guide permits multiple colors of a single shape for a single strength of a solid oral dosage form to be included in the same abbreviated antibiotic drug application. It is our intention to add a second capsule color to this AADA. The second capsule color will be marketed with a proprietary name (Vectrin®) and our originally approved capsule color will continue to be marketed under the generic name. Please note that this new color was obtained via the deletion of specific dye components from our currently approved product. In accordance with 21 CFR 314.70(d)(4), this change does not require prior FDA approval and will be reported in the next annual report. This submission strategy was confirmed via telephone conversation between myself and Mr. P. Rickman of your staff on October 31, 1996.

The purpose of this supplemental application is to provide the Office of Generic Drugs with the opportunity to review and approve labeling that bears the Vectrin brand name. In an October 31, 1996 telephone conversation with Mr. John Grace, also of your staff, I was instructed that this supplement should be submitted for prior approval. *While we believe that the regulations permit this change to be reported in the annual report (in accordance with 21 CFR 314.70(d)(2)), we wish to fully comply with Mr. Grace's recommendations. However, please note that we desire to implement this new labeling by February 28, 1997; therefore, we would appreciate any efforts that your staff can make in providing an expeditious review.*

Rockaway 80 Corporate Center • 100 Enterprise Drive • Suite 280 • Rockaway, NJ 07866 • 201-442-3233 • Fax: 201-442-3280

Please note that for completeness we have included a label for our bottles of 20 capsules package size. This size was originally approved as part of our initial AADA approval and was supported by completed stability studies. In pre-approval correspondence dated February 22, 1989, it was stated that the bottles of 20 capsules would be available for "Unit of Use" special contracts. We wish to have the option of using the unit of use bottles of 20 capsules for our Vectrin product. However, since this package size would not normally be commercially available, in accordance with 21 CFR 201.57(k)(2), we have not included the 20s package size on our proposed package insert.

Four copies of each of our draft labels and package insert labeling are provided in Attachments A through D. Please note that the attached labeling is identical to our currently approved labeling with the following modifications:

1) Addition of the Vectrin brand name and revised NDC numbers that are unique for the Vectrin product.

2) Revision of our company name and address to reflect the sale of Warner Chilcott by the Warner-Lambert Company and the subsequent relocation of our offices. (These actions were previously communicated to the AADA file in correspondence dated March 28, 1996 and November 21, 1996.)

3) In addition to the above items, the package insert bears revisions in the "Description" section (removal of dye components from the inactive ingredients listing) and in the "How Supplied" section (revised product description, color, imprint,etc.).

Finally, we would like to point out that the Vectrin trade name was in use many years ago by Parke-Davis, Division of Warner-Lambert Company, when they distributed minocycline hydrochloride capsules under a licensing agreement with Lederle Laboratories. Warner Chilcott, Inc. has obtained the exclusive rights to the use of the Vectrin trademark. Since the Vectrin name was previously used for this same product, we were hoping that any review conducted by FDA's naming committee, if needed at all, could be handled in an expedited manner.

If you should have any questions regarding this supplement, or require any additional information, please feel free to contact me at (201) 442-3233.

Sincerely,

Norma Enders

Norma A. Enders, R.Ph.
Sr. Director, Regulatory Affairs

approved
Lore
4/19/96

WARNER CHILCOTT
LABORATORIES
Division of Warner-Lambert Company

Sean Brennan, Ph.D.
Senior Director
Regulatory Affairs

Special Supplement -
Changes Being Effected

Douglas Sporn
Director, Office of Generic Drugs
Food and Drug Administration (CDER)
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAR 2 0 1996

REF. NO. SL-009

NDA SUPPL FOR Labeling Rev
SL-009 AI

MAR 2 1 1996

Re: AADA #63-067
Minocycline Hydrochloride Capsules USP, 100 mg
Labeling Supplement

Dear Mr. Sporn:

This is in response to your letter dated February 5, 1996 in which you commented on the labeling for our abbreviated antibiotic drug applications for Minocycline Hydrochloride Capsules USP, 50 mg and 100 mg.

In your letter, you requested that we revise our package insert labeling for the subject product in accordance with the approved labeling of Minocin® (Lederle Laboratories Division, revised December 1993; approved August 8, 1995).

We have completed these revisions and are submitting twelve copies of our final printed insert labeling in Attachment A for your review.

We trust that the enclosed labeling is satisfactory. We are concurrently submitting a similar supplement to our 50 mg strength application (AADA #63-066). If you should require any additional information, please do not hesitate to contact me at (201) 540-7181, or Norma Enders of my staff at (201) 540-4333.

Sincerely,

Norma Enders for

Sean Brennan, Ph. D.
Senior Director
Regulatory Affairs

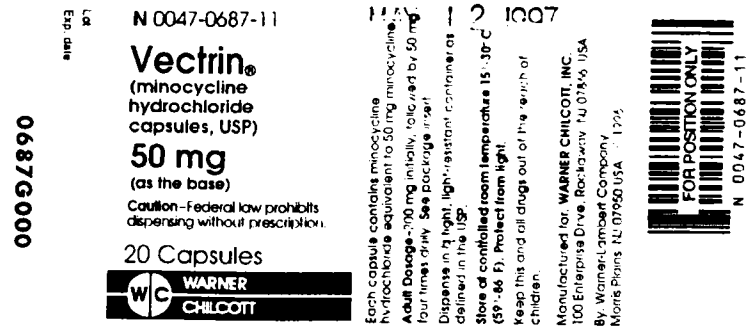
CENTER FOR DRUG EVALUATION AND RESEARCH

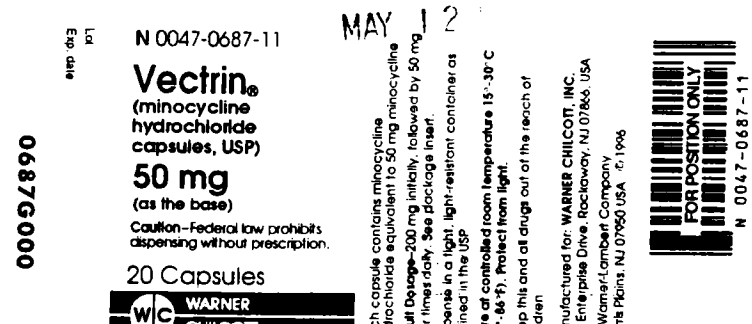
APPLICATION NUMBER 063066 /S011, 010, 009, 008, 007, 006

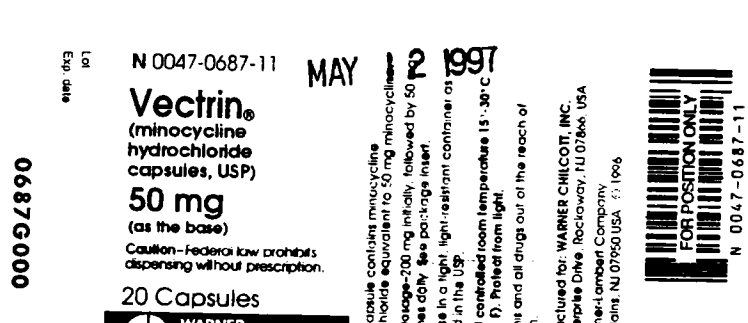
FINAL PRINTED LABELING

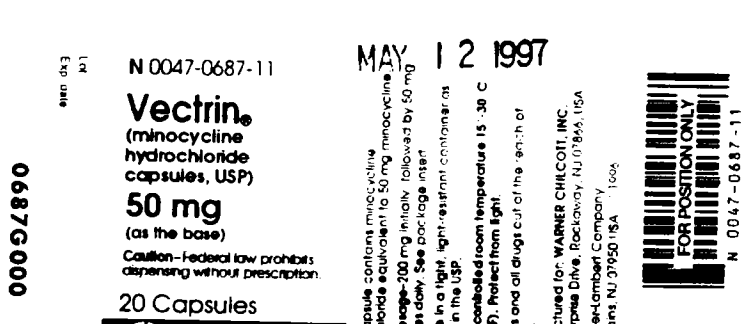
MHLG0

AADA #63-066 Minocycline HCl Capsules, USP, 50 mg Submission 4/21/97









FOR POSITION ONLY

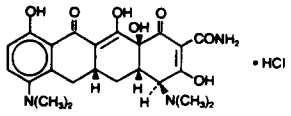
APPROVED

APR 24 1996

Minocycline HCl Capsules, USP

DESCRIPTION

Minocycline hydrochloride, a semisynthetic derivative of tetracycline, is [4 *S*-(4α,4aα, 5aα,12aα)]-4,7-Bis(dimethylamino)-1,4,4a, 5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride. Its structural formula is:



$C_{23}H_{27}N_3O_7 \cdot HCl$ M.W. 493.94

Each capsule, for oral administration, contains minocycline hydrochloride equivalent to 50 or 100 mg minocycline. In addition, each capsule contains the following inactive ingredients: magnesium stearate, NF and pregelatinized starch, NF (corn). The capsule shell contains black iron oxide; FD&C blue #1; gelatin, NF; silicon dioxide, NF; sodium lauryl sulfate, NF; titanium dioxide and yellow iron oxide. The 50-mg capsule shell also contains D&C red #28, D&C yellow #10, and FD&C red #40.

CLINICAL PHARMACOLOGY

Following oral administration of minocycline hydrochloride capsules, absorption from the gastrointestinal tract is rapid. Following a single dose of minocycline hydrochloride administered to normal fasting adult volunteers, maximum serum concentrations were attained in 1 to 4 hours. The serum half-life in normal volunteers ranged from approximately 11 hours to 22 hours.

When minocycline hydrochloride capsules were given concomitantly with a meal which included dairy products, the extent of absorption was not noticeably influenced. The peak plasma concentrations were slightly decreased and delayed by one hour when administered with food, compared to dosing under fasting conditions.

In previous studies with minocycline hydrochloride, the minocycline serum half-life ranged from 11 to 16 hours in 7 patients with hepatic dysfunction, and from 18 to 69 hours in 5 patients with renal dysfunction. The urinary and fecal recovery of minocycline when administered to 12 normal volunteers is one-half to one-third that of other tetracyclines.

Microbiology—The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. The tetracyclines, including minocycline, have similar antimicrobial spectra of activity against a wide range of gram-positive and gram-negative organisms. Cross-resistance of these organisms to tetracyclines is common.

While *in vitro* studies have demonstrated the susceptibility of most strains of the following microorganisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented.

GRAM-NEGATIVE BACTERIA:
Bartonella bacilliformis
Brucella species
Campylobacter fetus
Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzae
Listeria monocytogenes
Neisseria gonorrhoeae
Vibrio cholerae
Yersinia pestis

Because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility tests are especially recommended:

Acinetobacter species
Bacteroides species
Enterobacter aerogenes
Escherichia coli
Klebsiella species
Shigella species

[illegible] tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. The tetracyclines, including minocycline, have similar antimicrobial spectra of activity against a wide range of gram-positive and gram-negative organisms. Cross-resistance of these organisms to tetracyclines is common.

While *in vitro* studies have demonstrated the susceptibility of most strains of the following microorganisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented.

GRAM-NEGATIVE BACTERIA:
Bartonella bacilliformis
Brucella species
Campylobacter fetus
Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzae
Listeria monocytogenes
Neisseria gonorrhoeae
Vibrio cholerae
Yersinia pestis

Because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility tests are especially recommended:

Acinetobacter species
Bacteroides species
Enterobacter aerogenes
Escherichia coli
Klebsiella species
Shigella species

GRAM-POSITIVE BACTERIA:
Because many strains of the following groups of gram-positive microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are especially recommended. Up to 44 percent of *Streptococcus pyogenes* strains have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.

Alpha hemolytic streptococci (viridans group)
Streptococcus pneumoniae
Streptococcus pyogenes

OTHER MICROORGANISMS:
Actinomyces species
Bacillus anthracis
Balantidium coli
Borrelia recurrentis
Chlamydia psittaci
Chlamydia trachomatis
Clostridium species
Entamoeba species
Fusobacterium fusiforme
Propionibacterium acnes
Treponema pallidum
Treponema pertenue
Ureaplasma urealyticum

Susceptibility Tests
Diffusion Techniques—The use of antibiotic disk susceptibility test methods which measure zone diameter gives an accurate estimation of susceptibility of microorganisms to minocycline HCl. One such standard procedure[1] has been recommended for use with disks for testing antimicrobials. Either the 30 mcg tetracycline-class disk or the 30 mcg minocycline disk should be used for the determination of the susceptibility of microorganisms to minocycline.

With this type of procedure a report of "susceptible" from the laboratory indicates that the infecting organism is likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (eg, urine) in which high antibiotic levels are attained. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. With either the tetracycline-class disk or the minocycline disk, zone sizes of 19 mm or greater indicate susceptibility, zone sizes of 14 mm or less indicate resistance, and zone sizes of 15 to 18 mm indicate intermediate susceptibility.

Standardized procedures require the use of laboratory control organisms. The 30 mcg tetracycline disk should give zone diameters between 19 and 28 mm for *Staphylococcus aureus* ATCC 25923 and between 18 and 25 mm for *Escherichia coli* ATCC 25922. The 30 mcg minocycline disk should give zone diameters between 25 and 30 mm for *S. aureus* ATCC 25923 and between 19 and 25 mm for *E. coli* ATCC 25922.

Dilution Techniques—When using the NCCLS agar dilution or broth dilution (including microdilution) method[2] or equivalent, a bacterial isolate may be considered susceptible if the MIC (minimal inhibitory concentration) of minocycline is 4 mcg/mL or less. Organisms are considered resistant if the MIC is 16 mcg/mL or greater. Organisms with an MIC value of less than 16 mcg/mL but greater than 4 mcg/mL are expected to be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (eg, urine) in which high antibiotic levels are attained.

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard tetracycline or minocycline powder should give MIC values of 0.25 mcg/mL to 1.0 mcg/mL for *S. aureus* ATCC 25923, and 1.0 mcg/mL to 4.0 mcg/mL for *E. coli* ATCC 25922.

INDICATIONS AND USAGE

Minocycline hydrochloride capsules are indicated in the treatment of the following infections due to susceptible strains of the designated microorganisms:

Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox and tick fevers caused by Rickettsiae

if the infection is confined to tissues [illegible] (eg, urine) in which high antibiotic levels are attained.

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard tetracycline or minocycline powder should give MIC values of 0.25 mcg/mL to 1.0 mcg/mL for *S. aureus* ATCC 25923, and 1.0 mcg/mL to 4.0 mcg/mL for *E. coli* ATCC 25922.

INDICATIONS AND USAGE

Minocycline hydrochloride capsules are indicated in the treatment of the following infections due to susceptible strains of the designated microorganisms:

Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox and tick fevers caused by Rickettsiae.

Respiratory tract infections caused by *Mycoplasma pneumoniae*.

Lymphogranuloma venereum caused by *Chlamydia trachomatis*.

Psittacosis (ornithosis) due to *Chlamydia psittaci*.

Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated, as judged by immunofluorescence.

Inclusion conjunctivitis caused by *Chlamydia trachomatis*.

Nongonococcal urethritis in adults caused by *Ureaplasma urealyticum* or *Chlamydia trachomatis*.

Relapsing fever due to *Borrelia recurrentis*.

Chancroid caused by *Haemophilus ducreyi*.

Plague due to *Yersinia pestis*.

Tularemia due to *Francisella tularensis*.

Cholera caused by *Vibrio cholerae*.

Campylobacter fetus infections caused by *Campylobacter fetus*.

Brucellosis due to *Brucella* species (in conjunction with streptomycin).

Bartonellosis due to *Bartonella bacilliformis*.

Granuloma inguinale caused by *Calymmatobacterium granulomatis*.

Minocycline is indicated for treatment of infections caused by the following gram-negative microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Escherichia coli.

Enterobacter aerogenes.

Shigella species.

Acinetobacter species.

Respiratory tract infections caused by *Haemophilus influenzae*.

Respiratory tract and urinary tract infections caused by *Klebsiella* species.

Minocycline hydrochloride capsules are indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Upper respiratory tract infections caused by *Streptococcus pneumoniae*.

Skin and skin structure infections caused by *Staphylococcus aureus*. (Note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection.)

Uncomplicated urethritis in men due to *Neisseria gonorrhoeae* and for the treatment of other gonococcal infections when penicillin is contraindicated.

When penicillin is contraindicated, minocycline is an alternative drug in the treatment of the following infections:

Infections in women caused by *Neisseria gonorrhoeae*.

Syphilis caused by *Treponema pallidum*.

Yaws caused by *Treponema pertenue*.

Listeriosis due to *Listeria monocytogenes*.

Anthrax due to *Bacillus anthracis*.

Vincent's infection caused by *Fusobacterium fusiforme*.

Actinomycosis caused by *Actinomyces israeli*.

Infections caused by *Clostridium* species.

In *acute intestinal amebiasis*, minocycline may be a useful adjunct to amebicides.

In severe *acne*, minocycline may be useful adjunctive therapy.

Oral minocycline is indicated in the treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx. In order to preserve the usefulness of minocycline in the treatment of asymptomatic meningococcal carrier, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the prophylactic use of minocycline be reserved for situations in which the risk of meningococcal meningitis is high.

Oral minocycline is not indicated for the treatment of meningococcal infection.

Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline hydrochloride has been used successfully in the treatment of infections caused by *Mycobacterium marinum*.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

MINOCYCLINE HYDROCHLORIDE CAPSULES, LIKE OTHER TETRACYCLINE-CLASS

Acinetobacter species.

Respiratory tract infections caused by *Haemophilus influenzae*.

Respiratory tract and urinary tract infections caused by *Klebsiella* species.

Minocycline hydrochloride capsules are indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Upper respiratory tract infections caused by *Streptococcus pneumoniae*.

Skin and skin structure infections caused by *Staphylococcus aureus*. (Note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection.)

Uncomplicated urethritis in men due to *Neisseria gonorrhoeae* and for the treatment of other gonococcal infections when penicillin is contraindicated.

When penicillin is contraindicated, minocycline is an alternative drug in the treatment of the following infections:

Infections in women caused by *Neisseria gonorrhoeae*.

Syphilis caused by *Treponema pallidum*.

Yaws caused by *Treponema pertenue*.

Listeriosis due to *Listeria monocytogenes*.

Anthrax due to *Bacillus anthracis*.

Vincent's infection caused by *Fusobacterium fusiforme*.

Actinomycosis caused by *Actinomyces israelii*.

Infections caused by *Clostridium* species.

In *acute intestinal amebiasis*, minocycline may be a useful adjunct to amebicides.

In severe *acne*, minocycline may be useful adjunctive therapy.

Oral minocycline is indicated in the treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx. In order to preserve the usefulness of minocycline in the treatment of asymptomatic meningococcal carrier, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the prophylactic use of minocycline be reserved for situations in which the risk of meningococcal meningitis is high.

Oral minocycline is not indicated for the treatment of meningococcal infection.

Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline hydrochloride has been used successfully in the treatment of infections caused by *Mycobacterium marinum*.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

MINOCYCLINE HYDROCHLORIDE CAPSULES, LIKE OTHER TETRACYCLINE-CLASS ANTIBIOTICS, CAN CAUSE FETAL HARM WHEN ADMINISTERED TO A PREGNANT WOMAN. IF ANY TETRACYCLINE IS USED DURING PREGNANCY, OR IF THE PATIENT BECOMES PREGNANT WHILE TAKING THESE DRUGS,THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMA-

5

NENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN).

This adverse reaction is more common during long-term use of the drug but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED DURING TOOTH DEVELOPMENT UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in young animals (rats and rabbits) given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has been noted in animals treated early in pregnancy.

The antianabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated, and if therapy is prolonged, serum level determinations of the drug may be advisable.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This has been reported rarely with minocycline.

Central nervous system side effects including lightheadedness, dizziness, or vertigo have been reported with minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and usually disappear rapidly when the drug is discontinued.

PRECAUTIONS

General

As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

Pseudotumor cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracyclines. The usual clinical manifestations are headache and blurred vision. Bulging fontanels have been associated with the use of tetracyclines in infants. While both of these conditions and related symptoms usually resolve after discontinuation of the tetracycline, the possibility for permanent sequelae exists.

Incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy when indicated.

Information for Patients

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema. This reaction has been reported rarely with use of minocycline.

Patients who experience central nervous system symptoms (see WARNINGS) should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy.

Concurrent use of tetracycline may render oral contraceptives less effective (see Drug Interactions).

Laboratory Tests

In venereal disease when coexistent syphilis is suspected, a dark-field examination should be done before treatment is started and the blood serology repeated monthly for at least four months.

In long-term therapy, periodic laboratory evaluations of organ systems, including hematopoietic, renal, and hepatic studies should be performed.

Drug Interactions

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium or magnesium, and iron-containing preparations.

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

Concurrent use of tetracyclines may render oral contraceptives less effective.

Drug/Laboratory Test Interactions

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Dietary administration of minocycline in

[illegible]

Concurrent use of tetracyclines may render oral contraceptives less effective.

Drug/Laboratory Test Interactions
False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Dietary administration of minocycline in long-term tumorigenicity studies in rats resulted in evidence of thyroid tumor production. Minocycline has also been found to produce thyroid hyperplasia in rats and dogs. In addition, there has been evidence of oncogenic activity in rats in studies with a related antibiotic, oxytetracycline (ie, adrenal and pituitary tumors). Likewise, although mutagenicity studies of minocycline have not been conducted, positive results in *in vitro* mammalian cell assays (ie, mouse lymphoma and Chinese hamster lung cells) have been reported for related antibiotics (tetracycline hydrochloride and oxytetracycline). Segment I (fertility and general reproduction) studies have provided evidence that minocycline impairs fertility in male rats.

Teratogenic Effects: *Pregnancy:* Pregnancy Category D (see WARNINGS).

Labor and Delivery
The effect of tetracyclines on labor and delivery is unknown.

Nursing Mothers
Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from the tetracyclines, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (see WARNINGS).

Pediatric Use: see WARNINGS.

ADVERSE REACTIONS

Due to oral minocycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines.

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, pancreatitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, and increases in liver enzymes. Rarely, hepatitis and liver failure have been reported. Rare instances of esophagitis and esophageal ulcerations have been reported in patients taking the tetracycline-class antibiotics in capsule and tablet form. Most of these patients took the medication immediately before going to bed (see DOSAGE AND ADMINISTRATION).

Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Fixed drug eruptions, including balanitis, have been rarely reported. Erythema multiforme and rarely Stevens-Johnson syndrome have been reported. Photosensitivity is discussed above (see WARNINGS). Pigmentation of the skin and mucous membranes has been reported.

Renal toxicity: Elevations in BUN have been reported and are apparently dose related (see WARNINGS).

Hypersensitivity reactions: Urticaria, angioneurotic edema, polyarthralgia, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus and rarely pulmonary infiltrates with eosinophilia have been reported. A transient lupus-like syndrome has also been reported.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

Central nervous system: Bulging fontanels in infants and benign intracranial hypertension (pseudotumor cerebri) in adults (see PRECAUTIONS—General) have been reported.

Other: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid glands. Very rare cases of abnormal thyroid function have been reported.

Tooth discoloration in pediatric patients less than 8 years of age (see WARNINGS) and also, rarely, in adults have been reported. Decreased hearing has been rarely reported in patients on minocycline hydrochloride.

OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures.

DOSAGE AND ADMINISTRATION

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF MINOCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Minocycline hydrochloride capsules may be taken with or without food.

ADULTS: The usual dosage of minocycline hydrochloride capsules is 200 mg initially followed by 100 mg every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50 mg capsules may be given initially followed by one 50 mg capsule four times daily.

FOR PEDIATRIC POPULATION ABOVE 8 YEARS OF AGE: The usual dosage of minocycline hydrochloride capsules is 4 mg/kg initially followed by 2 mg/kg every 12 hours.

Uncomplicated gonococcal infections other than urethritis and anorectal infections in men: 200 mg initially, followed by 100 mg every 12 hours for a minimum of four days, with post-therapy cultures within 2 to 3 days.

In the treatment of uncomplicated gonococcal [illegible] 100 mg every 12 hours for five

hydrochloride capsules is 200 mg initially, followed by 100 mg every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50 mg capsules may be given initially followed by one 50 mg capsule four times daily.

FOR PEDIATRIC POPULATION ABOVE 8 YEARS OF AGE: The usual dosage of minocycline hydrochloride capsules is 4 mg/kg initially followed by 2 mg/kg every 12 hours.

Uncomplicated gonococcal infections other than urethritis and anorectal infections in men: 200 mg initially, followed by 100 mg every 12 hours for a minimum of four days, with post-therapy cultures within 2 to 3 days.

In the treatment of uncomplicated gonococcal urethritis in men, 100 mg every 12 hours for five days is recommended.

For the treatment of syphilis, the usual dosage of minocycline hydrochloride capsules should be administered over a period of 10 to 15 days. Close follow-up, including laboratory tests, is recommended.

In the treatment of meningococcal carrier state, the recommended dosage is 100 mg every 12 hours for five days.

Mycobacterium marinum infections: Although optimal doses have not been established, 100 mg every 12 hours for 6 to 8 weeks have been used successfully in a limited number of cases.

Uncomplicated nongonococcal urethral infection in adults caused by *Chlamydia trachomatis* or *Ureaplasma urealyticum:* 100 mg orally, every 12 hours for at least seven days.

Ingestion of adequate amounts of fluids along with capsule and tablet forms of drugs in the tetracycline-class is recommended to reduce the risk of esophageal irritation and ulceration.

In patients with renal impairment (see WARNINGS) the total dosage should be decreased by either reducing the recommended individual doses and/or by extending the time intervals between doses.

HOW SUPPLIED

Minocycline hydrochloride capsules USP, equivalent to 50 mg or 100 mg minocycline, are supplied as:

50 mg olive and brown, size #3, capsules imprinted WC 615:
Bottles of 100 N 0047-0615-24
Bottles of 1000 N 0047-0615-32

100 mg white and olive, size #2, capsules imprinted WC 616:
Bottles of 50 N 0047-0616-19
Bottles of 1000 N 0047-0616-32

Storage Conditions: Store at controlled room temperature 15°-30° C (59°-86° F). Protect from light.

Caution—Federal law prohibits dispensing without prescription.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Minocycline HCl has been observed to cause a dark discoloration of the thyroid in experimental animals (rats, minipigs, dogs, and monkeys). In the rat, chronic treatment with minocycline hydrochloride has resulted in goiter accompanied by elevated radioactive iodine uptake and evidence of thyroid tumor production. Minocycline hydrochloride has also been found to produce thyroid hyperplasia in rats and dogs.

REFERENCES

1. National Committee for Clinical Laboratory Standards, Approved Standard: *Performance Standards for Antimicrobial Disk Susceptibility Tests*, 3rd Edition, Vol. 4(16): M2-A3, Villanova, PA. December 1984.

2. National Committee for Clinical Laboratory Standards, Approved Standard: *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, 2nd Edition, Vol. 5(22): M7-A, Villanova, PA. December 1985.

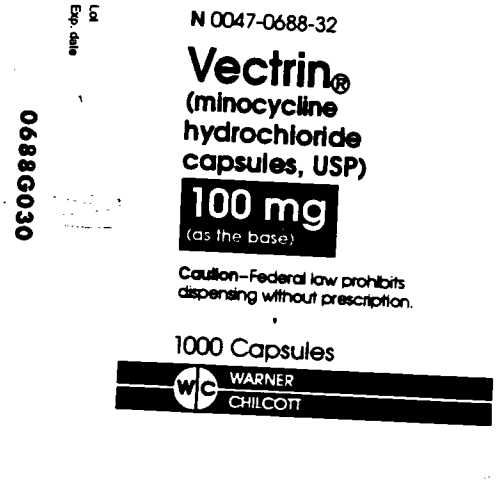
0615G025

Revised February 1996

WARNER CHILCOTT LABS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

APR 14 1997

APR 14 1997



APR 14 1997

Vectrin®
(minocycline hydrochloride capsules, USP)
0687G010

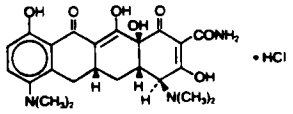
FOR POSITION ONLY

Vectrin®

(minocycline hydrochloride capsules, USP)

DESCRIPTION

Minocycline hydrochloride, a semisynthetic derivative of tetracycline, is [4 *S*-(4α,4aα, 5aα,12aα)]-4,7-Bis(dimethylamino)-1,4,4a, 5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride. Its structural formula is:



$C_{23}H_{27}N_3O_7 \cdot HCl$ M.W. 493.94

Each Vectrin capsule, for oral administration, contains minocycline hydrochloride equivalent to 50 or 100 mg minocycline. In addition, each capsule contains the following inactive ingredients: magnesium stearate, NF and pregelatinized starch, NF (corn). The capsule shell contains gelatin, NF; silicon dioxide, NF; sodium lauryl sulfate, NF; and titanium dioxide. The 50-mg capsule shell also contains D&C yellow #10, and FD&C red #40. The 100-mg capsule shell also contains FD&C blue #1.

CLINICAL PHARMACOLOGY

Following oral administration of minocycline hydrochloride capsules, absorption from the gastrointestinal tract is rapid. Following a single dose of minocycline hydrochloride administered to normal fasting adult volunteers, maximum serum concentrations were attained in 1 to 4 hours. The serum half-life in normal volunteers ranged from approximately 11 hours to 22 hours.

When minocycline hydrochloride capsules were given concomitantly with a meal which included dairy products, the extent of absorption was not noticeably influenced. The peak plasma concentrations were slightly decreased and delayed by one hour when administered with food, compared to dosing under fasting conditions.

In previous studies with minocycline hydrochloride, the minocycline serum half-life ranged from 11 to 16 hours in 7 patients with hepatic dysfunction, and from 18 to 69 hours in 5 patients with renal dysfunction. The urinary and fecal recovery of minocycline when administered to 12 normal volunteers is one-half to one-third that of other tetracyclines.

Microbiology—The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. The tetracyclines, including minocycline, have similar antimicrobial spectra of activity against a wide range of gram-positive and gram-negative organisms. Cross-resistance of these organisms to tetracyclines is common.

While *in vitro* studies have demonstrated the susceptibility of most strains of the following microorganisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented.

GRAM-NEGATIVE BACTERIA:
Bartonella bacilliformis
Brucella species
Campylobacter fetus
Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzae
Listeria monocytogenes
Neisseria gonorrhoeae
Vibrio cholerae
Yersinia pestis

Because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility tests are especially recommended:

Acinetobacter species
Bacteroides species
Enterobacter aerogenes

2

these organisms is reliably [illegible]

While *in vitro* studies have demonstrated the susceptibility of most strains of the following microorganisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented.

GRAM-NEGATIVE BACTERIA:
Bartonella bacilliformis
Brucella species
Campylobacter fetus
Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzae
Listeria monocytogenes
Neisseria gonorrhoeae
Vibrio cholerae
Yersinia pestis

Because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility tests are especially recommended:

Acinetobacter species
Bacteroides species
Enterobacter aerogenes
Escherichia coli
Klebsiella species
Shigella species

GRAM-POSITIVE BACTERIA:
Because many strains of the following groups of gram-positive microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are especially recommended. Up to 44 percent of *Streptococcus pyogenes* strains have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.

Alpha hemolytic streptococci (viridans group)
Streptococcus pneumoniae
Streptococcus pyogenes

OTHER MICROORGANISMS:
Actinomyces species
Bacillus anthracis
Balantidium coli
Borrelia recurrentis
Chlamydia psittaci
Chlamydia trachomatis
Clostridium species
Entamoeba species
Fusobacterium fusiforme
Propionibacterium acnes
Treponema pallidum
Treponema pertenue
Ureaplasma urealyticum

Susceptibility Tests
Diffusion Techniques—The use of antibiotic disk susceptibility test methods which measure zone diameter gives an accurate estimation of susceptibility of microorganisms to minocycline HCl. One such standard procedure[1] has been recommended for use with disks for testing antimicrobials. Either the 30 mcg tetracycline-class disk or the 30 mcg minocycline disk should be used for the determination of the susceptibility of microorganisms to minocycline. With this type of procedure a report of "susceptible" from the laboratory indicates that the infecting organism is likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (eg, urine) in which high antibiotic levels are attained. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. With either the tetracycline-class disk or the minocycline disk, zone sizes of 19 mm or greater indicate susceptibility, zone sizes of 14 mm or less indicate resistance, and zone sizes of 15 to 18 mm indicate intermediate susceptibility.

Standardized procedures require the use of laboratory control organisms. The 30 mcg tetracycline disk should give zone diameters between 19 and 28 mm for *Staphylococcus aureus* ATCC 25923 and between 18 and 25 mm for *Escherichia coli* ATCC 25922. The 30 mcg minocycline disk should give zone diameters between 25 and 30 mm for *S. aureus* ATCC 25923 and between 19 and 25 mm for *E. coli* ATCC 25922.

Dilution Techniques—When using the NCCLS agar dilution or broth dilution (including microdilution) method[2] or equivalent, a bacterial isolate may be considered susceptible if the MIC (minimal inhibitory concentration) of minocycline is 4 mcg/mL or less. Organisms are considered resistant if the MIC is 16 mcg/mL or greater. Organisms with an MIC value of less than 16 mcg/mL but greater than 4 mcg/mL are expected to be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (eg, urine) in which high antibiotic levels are attained.

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard tetracycline or minocycline powder should give MIC values of 0.25 mcg/mL to 1.0 mcg/mL for *S. aureus* ATCC 25923, and 1.0 mcg/mL to 4.0 mcg/mL for *E. coli* ATCC 25922.

INDICATIONS AND USAGE

Vectrin capsules are indicated in the treatment of the following infections due to susceptible strains of the designated microorganisms:

Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox and tick fevers caused by Rickettsiae.

Respiratory tract infections caused by *Mycoplasma pneumoniae*.

Lymphogranuloma venereum caused by *Chlamydia trachomatis*.

Psittacosis (ornithosis) due to *Chlamydia psittaci*.

1.0 mcg/mL to 4.0 mcg/mL for *E. coli* ATCC 25922.

INDICATIONS AND USAGE

Vectrin capsules are indicated in the treatment of the following infections due to susceptible strains of the designated microorganisms:

Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox and tick fevers caused by Rickettsiae.

Respiratory tract infections caused by *Mycoplasma pneumoniae*.

Lymphogranuloma venereum caused by *Chlamydia trachomatis*.

Psittacosis (ornithosis) due to *Chlamydia psittaci*.

Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated, as judged by immunofluorescence.

Inclusion conjunctivitis caused by *Chlamydia trachomatis*.

Nongonococcal urethritis in adults caused by *Ureaplasma urealyticum* or *Chlamydia trachomatis*.

Relapsing fever due to *Borrelia recurrentis*.

Chancroid caused by *Haemophilus ducreyi*.

Plague due to *Yersinia pestis*.

Tularemia due to *Francisella tularensis*.

Cholera caused by *Vibrio cholerae*.

Campylobacter fetus infections caused by *Campylobacter fetus*.

Brucellosis due to *Brucella* species (in conjunction with streptomycin).

Bartonellosis due to *Bartonella bacilliformis*.

Granuloma inguinale caused by *Calymmatobacterium granulomatis*.

Minocycline is indicated for treatment of infections caused by the following gram-negative microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Escherichia coli.

Enterobacter aerogenes.

Shigella species.

Acinetobacter species.

Respiratory tract infections caused by *Haemophilus influenzae*.

Respiratory tract and urinary tract infections caused by *Klebsiella* species.

Vectrin capsules are indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Upper respiratory tract infections caused by *Streptococcus pneumoniae*.

Skin and skin structure infections caused by *Staphylococcus aureus*. (Note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection.)

Uncomplicated urethritis in men due to *Neisseria gonorrhoeae* and for the treatment of other gonococcal infections when penicillin is contraindicated.

When penicillin is contraindicated, minocycline is an alternative drug in the treatment of the following infections:

Infections in women caused by *Neisseria gonorrhoeae*.

Syphilis caused by *Treponema pallidum*.

Yaws caused by *Treponema pertenue*.

Listeriosis due to *Listeria monocytogenes*.

Anthrax due to *Bacillus anthracis*.

Vincent's infection caused by *Fusobacterium fusiforme*.

Actinomycosis caused by *Actinomyces israelii*.

Infections caused by *Clostridium* species.

In *acute intestinal amebiasis*, minocycline may be a useful adjunct to amebicides.

In severe *acne*, Vectrin may be useful adjunctive therapy.

Oral minocycline is indicated in the treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx. In order to preserve the usefulness of minocycline in the treatment of asymptomatic meningococcal carrier, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the prophylactic use of minocycline be reserved for situations in which the risk of meningococcal meningitis is high.

Oral minocycline is not indicated for the treatment of meningococcal infection.

Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline hydrochloride has been used successfully in the treatment of infections caused by *Mycobacterium marinum*.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

VECTRIN CAPSULES, LIKE OTHER TETRACYCLINE-CLASS ANTIBIOTICS, CAN CAUSE FETAL HARM WHEN ADMINISTERED TO A PREGNANT WOMAN. IF ANY TETRACYCLINE IS USED DURING PREGNANCY, OR IF THE PATIENT BECOMES PREGNANT WHILE TAKING THESE DRUGS, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. THE USE OF [illegible] TETRACYCLINE CLASS

Respiratory tract infections caused by *Haemophilus influenzae*.

Respiratory tract and urinary tract infections caused by *Klebsiella* species.

Vectrin capsules are indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Upper respiratory tract infections caused by *Streptococcus pneumoniae*.

Skin and skin structure infections caused by *Staphylococcus aureus*. (Note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection.)

Uncomplicated urethritis in men due to *Neisseria gonorrhoeae* and for the treatment of other gonococcal infections when penicillin is contraindicated.

When penicillin is contraindicated, minocycline is an alternative drug in the treatment of the following infections:

Infections in women caused by *Neisseria gonorrhoeae*.

Syphilis caused by *Treponema pallidum*.

Yaws caused by *Treponema pertenue*.

Listeriosis due to *Listeria monocytogenes*.

Anthrax due to *Bacillus anthracis*.

Vincent's infection caused by *Fusobacterium fusiforme*.

Actinomycosis caused by *Actinomyces israelii*.

Infections caused by *Clostridium* species.

In *acute intestinal amebiasis*, minocycline may be a useful adjunct to amebicides.

In severe *acne*, Vectrin may be useful adjunctive therapy.

Oral minocycline is indicated in the treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx. In order to preserve the usefulness of minocycline in the treatment of asymptomatic meningococcal carrier, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the prophylactic use of minocycline be reserved for situations in which the risk of meningococcal meningitis is high.

Oral minocycline is not indicated for the treatment of meningococcal infection.

Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline hydrochloride has been used successfully in the treatment of infections caused by *Mycobacterium marinum*.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

VECTRIN CAPSULES, LIKE OTHER TETRACYCLINE-CLASS ANTIBIOTICS, CAN CAUSE FETAL HARM WHEN ADMINISTERED TO A PREGNANT WOMAN. IF ANY TETRACYCLINE IS USED DURING PREGNANCY, OR IF THE PATIENT BECOMES PREGNANT WHILE TAKING THESE DRUGS, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN).

WC WARNER CHILCOTT

5

This adverse reaction is more common during long-term use of the drug but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED DURING TOOTH DEVELOPMENT UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in young animals (rats and rabbits) given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has been noted in animals treated early in pregnancy.

The antianabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated, and if therapy is prolonged, serum level determinations of the drug may be advisable.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This has been reported rarely with minocycline.

Central nervous system side effects including lightheadedness, dizziness, or vertigo have been reported with minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and usually disappear rapidly when the drug is discontinued.

PRECAUTIONS

General

As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

Pseudotumor cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracyclines. The usual clinical manifestations are headache and blurred vision. Bulging fontanels have been associated with the use of tetracyclines in infants. While both of these conditions and related symptoms usually resolve after discontinuation of the tetracycline, the possibility for permanent sequelae exists.

Incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy when indicated.

Information for Patients

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema. This reaction has been reported rarely with use of minocycline.

Patients who experience central nervous system symptoms (see WARNINGS) should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy.

Concurrent use of tetracycline may render oral contraceptives less effective (see Drug Interactions).

Laboratory Tests

In venereal disease when coexistent syphilis is suspected, a dark-field examination should be done before treatment is started and the blood serology repeated monthly for at least four months.

In long-term therapy, periodic laboratory evaluations of organ systems, including hematopoietic, renal, and hepatic studies should be performed.

Drug Interactions

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium or magnesium, and iron-containing preparations.

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

Concurrent use of tetracyclines may render oral contraceptives less effective.

Drug/Laboratory Test Interactions

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Dietary administration of minocycline in long-term tumorigenicity studies in rats resulted in evidence of thyroid tumor production.

Drug/Laboratory Test Interactions
False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Dietary administration of minocycline in long-term tumorigenicity studies in rats resulted in evidence of thyroid tumor production. Minocycline has also been found to produce thyroid hyperplasia in rats and dogs. In addition, there has been evidence of oncogenic activity in rats in studies with a related antibiotic, oxytetracycline (ie, adrenal and pituitary tumors). Likewise, although mutagenicity studies of minocycline have not been conducted, positive results in *in vitro* mammalian cell assays (ie, mouse lymphoma and Chinese hamster lung cells) have been reported for related antibiotics (tetracycline hydrochloride and oxytetracycline). Segment I (fertility and general reproduction) studies have provided evidence that minocycline impairs fertility in male rats.

Teratogenic Effects: *Pregnancy*: Pregnancy Category D (see WARNINGS).

Labor and Delivery
The effect of tetracyclines on labor and delivery is unknown.

Nursing Mothers
Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from the tetracyclines, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (see WARNINGS).

Pediatric Use: see WARNINGS.

ADVERSE REACTIONS

Due to oral minocycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines.

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, pancreatitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, and increases in liver enzymes. Rarely, hepatitis and liver failure have been reported. Rare instances of esophagitis and esophageal ulcerations have been reported in patients taking the tetracycline-class antibiotics in capsule and tablet form. Most of these patients took the medication immediately before going to bed (see DOSAGE AND ADMINISTRATION).

Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Fixed drug eruptions, including balanitis, have been rarely reported. Erythema multiforme and rarely Stevens-Johnson syndrome have been reported. Photosensitivity is discussed above (see WARNINGS). Pigmentation of the skin and mucous membranes has been reported.

Renal toxicity: Elevations in BUN have been reported and are apparently dose related (see WARNINGS).

Hypersensitivity reactions: Urticaria, angioneurotic edema, polyarthralgia, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus and rarely pulmonary infiltrates with eosinophilia have been reported. A transient lupus-like syndrome has also been reported.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

Central nervous system: Bulging fontanels in infants and benign intracranial hypertension (pseudotumor cerebri) in adults (see PRECAUTIONS—General) have been reported.

Other: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid glands. Very rare cases of abnormal thyroid function have been reported.

Tooth discoloration in pediatric patients less than 8 years of age (see WARNINGS) and also, rarely, in adults have been reported. Decreased hearing has been rarely reported in patients on minocycline hydrochloride.

OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures.

DOSAGE AND ADMINISTRATION

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF MINOCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Minocycline hydrochloride capsules may be taken with or without food.

ADULTS: The usual dosage of Vectrin (minocycline hydrochloride capsules) is 200 mg initially followed by 100 mg every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50 mg capsules may be given initially followed by one 50 mg capsule four times daily.

FOR PEDIATRIC POPULATION ABOVE 8 YEARS OF AGE: The usual dosage of Vectrin (minocycline hydrochloride capsules) is 4 mg/kg initially followed by 2 mg/kg every 12 hours.

Uncomplicated gonococcal infections other than urethritis and anorectal infections in men: 200 mg initially, followed by 100 mg every 12 hours for a minimum of four days, with post-therapy cultures within 2 to 3 days.

In the treatment of uncomplicated gonococcal urethritis in men, 100 mg every 12 hours for five days is recommended.

...dosage

FOR PEDIATRIC POPULATION ABOVE 8 YEARS OF AGE: The usual dosage of Vectrin (minocycline hydrochloride capsules) is 4 mg/kg initially followed by 2 mg/kg every 12 hours.

Uncomplicated gonococcal infections other than urethritis and anorectal infections in men: 200 mg initially, followed by 100 mg every 12 hours for a minimum of four days, with post-therapy cultures within 2 to 3 days.

In the treatment of uncomplicated gonococcal urethritis in men, 100 mg every 12 hours for five days is recommended.

For the treatment of syphilis, the usual dosage of Vectrin (minocycline hydrochloride capsules) should be administered over a period of 10 to 15 days. Close follow-up, including laboratory tests, is recommended.

In the treatment of meningococcal carrier state, the recommended dosage is 100 mg every 12 hours for five days.

Mycobacterium marinum infections: Although optimal doses have not been established, 100 mg every 12 hours for 6 to 8 weeks have been used successfully in a limited number of cases.

Uncomplicated nongonococcal urethral infection in adults caused by *Chlamydia trachomatis* or *Ureaplasma urealyticum*: 100 mg orally, every 12 hours for at least seven days.

Ingestion of adequate amounts of fluids along with capsule and tablet forms of drugs in the tetracycline-class is recommended to reduce the risk of esophageal irritation and ulceration.

In patients with renal impairment (see WARNINGS) the total dosage should be decreased by either reducing the recommended individual doses and/or by extending the time intervals between doses.

HOW SUPPLIED

Vectrin (minocycline hydrochloride capsules USP), equivalent to 50 mg or 100 mg minocycline, are supplied as:

50 mg orange opaque, size #3, capsules imprinted Vectrin 50 mg:
Bottles of 100 N 0047-0687-24
Bottles of 1000 N 0047-0687-32

100 mg blue opaque, size #2, capsules imprinted Vectrin 100 mg:
Bottles of 50 N 0047-0688-19
Bottles of 1000 N 0047-0688-32

Storage Conditions: Store at controlled room temperature 15°-30° C (59°-86° F). Protect from light.

Caution—Federal law prohibits dispensing without prescription.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Minocycline HCl has been observed to cause a dark discoloration of the thyroid in experimental animals (rats, minipigs, dogs, and monkeys). In the rat, chronic treatment with minocycline hydrochloride has resulted in goiter accompanied by elevated radioactive iodine uptake and evidence of thyroid tumor production. Minocycline hydrochloride has also been found to produce thyroid hyperplasia in rats and dogs.

REFERENCES

1. National Committee for Clinical Laboratory Standards, Approved Standard: *Performance Standards for Antimicrobial Disk Susceptibility Tests*, 3rd Edition, Vol. 4(16): M2-A3, Villanova, PA. December 1984.

2. National Committee for Clinical Laboratory Standards, Approved Standard: *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, 2nd Edition, Vol. 5(22): M7-A, Villanova, PA. December 1985.

0687G010

Issued November 1996

Manufactured for:
WARNER CHILCOTT, INC.
100 Enterprise Drive
Rockaway, NJ 07866 USA

By: Warner-Lambert Company
Morris Plains, NJ 07950 USA

FOR POSITION ONLY

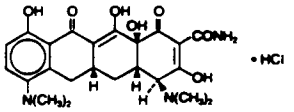
APPROVED

APR 24 1996

Minocycline HCl Capsules, USP

DESCRIPTION

Minocycline hydrochloride, a semisynthetic derivative of tetracycline, is [4 *S*-(4α,4aα, 5aα,12aα)]-4,7-Bis(dimethylamino)-1,4,4a, 5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride. Its structural formula is:



$C_{23}H_{27}N_3O_7 \cdot HCl$ M.W. 493.94

Each capsule, for oral administration, contains minocycline hydrochloride equivalent to 50 or 100 mg minocycline. In addition, each capsule contains the following inactive ingredients: magnesium stearate, NF and pregelatinized starch, NF (corn). The capsule shell contains black iron oxide; FD&C blue #1; gelatin, NF; silicon dioxide, NF; sodium lauryl sulfate, NF; titanium dioxide and yellow iron oxide. The 50-mg capsule shell also contains D&C red #28, D&C yellow #10, and FD&C red #40.

CLINICAL PHARMACOLOGY

Following oral administration of minocycline hydrochloride capsules, absorption from the gastrointestinal tract is rapid. Following a single dose of minocycline hydrochloride administered to normal fasting adult volunteers, maximum serum concentrations were attained in 1 to 4 hours. The serum half-life in normal volunteers ranged from approximately 11 hours to 22 hours.

When minocycline hydrochloride capsules were given concomitantly with a meal which included dairy products, the extent of absorption was not noticeably influenced. The peak plasma concentrations were slightly decreased and delayed by one hour when administered with food, compared to dosing under fasting conditions.

In previous studies with minocycline hydrochloride, the minocycline serum half-life ranged from 11 to 16 hours in 7 patients with hepatic dysfunction, and from 18 to 69 hours in 5 patients with renal dysfunction. The urinary and fecal recovery of minocycline when administered to 12 normal volunteers is one-half to one-third that of other tetracyclines.

Microbiology—The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. The tetracyclines, including minocycline, have similar antimicrobial spectra of activity against a wide range of gram-positive and gram-negative organisms. Cross-resistance of these organisms to tetracyclines is common.

While *in vitro* studies have demonstrated the susceptibility of most strains of the following microorganisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented.

GRAM-NEGATIVE BACTERIA:
Bartonella bacilliformis
Brucella species
Campylobacter fetus
Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzae
Listeria monocytogenes
Neisseria gonorrhoeae
Vibrio cholerae
Yersinia pestis

Because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility tests are especially recommended:

Acinetobacter species
Bacteroides species
Enterobacter aerogenes
Escherichia coli
Klebsiella species
Shigella species

GRAM-POSITIVE BACTERIA:
Because many strains of the following groups of gram-positive microorganisms have been

Vibrio cholerae
Yersinia pestis

Because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility tests are especially recommended:

Acinetobacter species
Bacteroides species
Enterobacter aerogenes
Escherichia coli
Klebsiella species
Shigella species

GRAM-POSITIVE BACTERIA:
Because many strains of the following groups of gram-positive microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are especially recommended. Up to 44 percent of *Streptococcus pyogenes* strains have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.

Alpha hemolytic streptococci (viridans group)
Streptococcus pneumoniae
Streptococcus pyogenes

OTHER MICROORGANISMS:
Actinomyces species
Bacillus anthracis
Balantidium coli
Borrelia recurrentis
Chlamydia psittaci
Chlamydia trachomatis
Clostridium species
Entamoeba species
Fusobacterium fusiforme
Propionibacterium acnes
Treponema pallidum
Treponema pertenue
Ureaplasma urealyticum

Susceptibility Tests
Diffusion Techniques—The use of antibiotic disk susceptibility test methods which measure zone diameter gives an accurate estimation of susceptibility of microorganisms to minocycline HCl. One such standard procedure[1] has been recommended for use with disks for testing antimicrobials. Either the 30 mcg tetracycline-class disk or the 30 mcg minocycline disk should be used for the determination of the susceptibility of microorganisms to minocycline.

With this type of procedure a report of "susceptible" from the laboratory indicates that the infecting organism is likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (eg, urine) in which high antibiotic levels are attained. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. With either the tetracycline-class disk or the minocycline disk, zone sizes of 19 mm or greater indicate susceptibility, zone sizes of 14 mm or less indicate resistance, and zone sizes of 15 to 18 mm indicate intermediate susceptibility.

Standardized procedures require the use of laboratory control organisms. The 30 mcg tetracycline disk should give zone diameters between 19 and 28 mm for *Staphylococcus aureus* ATCC 25923 and between 18 and 25 mm for *Escherichia coli* ATCC 25922. The 30 mcg minocycline disk should give zone diameters between 25 and 30 mm for *S. aureus* ATCC 25923 and between 19 and 25 mm for *E. coli* ATCC 25922.

Dilution Techniques—When using the NCCLS agar dilution or broth dilution (including microdilution) method[2] or equivalent, a bacterial isolate may be considered susceptible if the MIC (minimal inhibitory concentration) of minocycline is 4 mcg/mL or less. Organisms are considered resistant if the MIC is 16 mcg/mL or greater. Organisms with an MIC value of less than 16 mcg/mL but greater than 4 mcg/mL are expected to be susceptible if a high dosage is used or if the infection is confined to tissues and fluids (eg, urine) in which high antibiotic levels are attained.

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard tetracycline or minocycline powder should give MIC values of 0.25 mcg/mL to 1.0 mcg/mL for *S. aureus* ATCC 25923, and 1.0 mcg/mL to 4.0 mcg/mL for *E. coli* ATCC 25922.

INDICATIONS AND USAGE

Minocycline hydrochloride capsules are indicated in the treatment of the following infections due to susceptible strains of the designated microorganisms:

Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox and tick fevers caused by Rickettsiae.

Respiratory tract infections caused by *Mycoplasma pneumoniae*.

Lymphogranuloma venereum caused by *Chlamydia trachomatis*.

Psittacosis (ornithosis) due to *Chlamydia psittaci*.

Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated, as judged by immunofluorescence.

Inclusion conjunctivitis caused by *Chlamydia trachomatis*.

Nongonococcal urethritis in adults caused by *Ureaplasma urealyticum* or *Chlamydia trachomatis*.

Relapsing fever due to *Borrelia recurrentis*.

Chancroid caused by *Haemophilus ducreyi*.

Plague due to *Yersinia pestis*.

INDICATIONS AND USAGE

Minocycline hydrochloride capsules are indicated in the treatment of the following infections due to susceptible strains of the designated microorganisms:

Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox and tick fevers caused by Rickettsiae.

Respiratory tract infections caused by *Mycoplasma pneumoniae*.

Lymphogranuloma venereum caused by *Chlamydia trachomatis*.

Psittacosis (ornithosis) due to *Chlamydia psittaci*.

Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated, as judged by immunofluorescence.

Inclusion conjunctivitis caused by *Chlamydia trachomatis*.

Nongonococcal urethritis in adults caused by *Ureaplasma urealyticum* or *Chlamydia trachomatis*.

Relapsing fever due to *Borrelia recurrentis*.

Chancroid caused by *Haemophilus ducreyi*.

Plague due to *Yersinia pestis*.

Tularemia due to *Francisella tularensis*.

Cholera caused by *Vibrio cholerae*.

Campylobacter fetus infections caused by *Campylobacter fetus*.

Brucellosis due to *Brucella* species (in conjunction with streptomycin).

Bartonellosis due to *Bartonella bacilliformis*.

Granuloma inguinale caused by *Calymmatobacterium granulomatis*.

Minocycline is indicated for treatment of infections caused by the following gram-negative microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Escherichia coli.

Enterobacter aerogenes.

Shigella species.

Acinetobacter species.

Respiratory tract infections caused by *Haemophilus influenzae*.

Respiratory tract and urinary tract infections caused by *Klebsiella* species.

Minocycline hydrochloride capsules are indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Upper respiratory tract infections caused by *Streptococcus pneumoniae*.

Skin and skin structure infections caused by *Staphylococcus aureus*. (Note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection.)

Uncomplicated urethritis in men due to *Neisseria gonorrhoeae* and for the treatment of other gonococcal infections when penicillin is contraindicated.

When penicillin is contraindicated, minocycline is an alternative drug in the treatment of the following infections:

Infections in women caused by *Neisseria gonorrhoeae*.

Syphilis caused by *Treponema pallidum*.

Yaws caused by *Treponema pertenue*.

Listeriosis due to *Listeria monocytogenes*.

Anthrax due to *Bacillus anthracis*.

Vincent's infection caused by *Fusobacterium fusiforme*.

Actinomycosis caused by *Actinomyces israelii*.

Infections caused by *Clostridium* species.

In *acute intestinal amebiasis*, minocycline may be a useful adjunct to amebicides.

In severe acne, minocycline may be useful adjunctive therapy.

Oral minocycline is indicated in the treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx. In order to preserve the usefulness of minocycline in the treatment of asymptomatic meningococcal carrier, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the prophylactic use of minocycline be reserved for situations in which the risk of meningococcal meningitis is high.

Oral minocycline is not indicated for the treatment of meningococcal infection.

Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline hydrochloride has been used successfully in the treatment of infections caused by *Mycobacterium marinum*.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

MINOCYCLINE HYDROCHLORIDE CAPSULES, LIKE OTHER TETRACYCLINE-CLASS ANTIBIOTICS, CAN CAUSE FETAL HARM WHEN ADMINISTERED TO A PREGNANT WOMAN. IF ANY TETRACYCLINE IS USED DURING PREGNANCY, OR IF THE PATIENT BECOMES PREGNANT WHILE TAKING THESE DRUGS, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH

~~Acinetobacter species~~

Respiratory tract infections caused by *Haemophilus influenzae*.

Respiratory tract and urinary tract infections caused by *Klebsiella* species.

Minocycline hydrochloride capsules are indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Upper respiratory tract infections caused by *Streptococcus pneumoniae*.

Skin and skin structure infections caused by *Staphylococcus aureus*. (Note: Minocycline is not the drug of choice in the treatment of any type of staphylococcal infection.)

Uncomplicated urethritis in men due to *Neisseria gonorrhoeae* and for the treatment of other gonococcal infections when penicillin is contraindicated.

When penicillin is contraindicated, minocycline is an alternative drug in the treatment of the following infections:

Infections in women caused by *Neisseria gonorrhoeae*.

Syphilis caused by *Treponema pallidum*.

Yaws caused by *Treponema pertenue*.

Listeriosis due to *Listeria monocytogenes*.

Anthrax due to *Bacillus anthracis*.

Vincent's infection caused by *Fusobacterium fusiforme*.

Actinomycosis caused by *Actinomyces israelii*.

Infections caused by *Clostridium* species.

In *acute intestinal amebiasis*, minocycline may be a useful adjunct to amebicides.

In severe *acne*, minocycline may be useful adjunctive therapy.

Oral minocycline is indicated in the treatment of asymptomatic carriers of *Neisseria meningitidis* to eliminate meningococci from the nasopharynx. In order to preserve the usefulness of minocycline in the treatment of asymptomatic meningococcal carrier, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the prophylactic use of minocycline be reserved for situations in which the risk of meningococcal meningitis is high.

Oral minocycline is not indicated for the treatment of meningococcal infection.

Although no controlled clinical efficacy studies have been conducted, limited clinical data show that oral minocycline hydrochloride has been used successfully in the treatment of infections caused by *Mycobacterium marinum*.

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

MINOCYCLINE HYDROCHLORIDE CAPSULES, LIKE OTHER TETRACYCLINE-CLASS ANTIBIOTICS, CAN CAUSE FETAL HARM WHEN ADMINISTERED TO A PREGNANT WOMAN. IF ANY TETRACYCLINE IS USED DURING PREGNANCY, OR IF THE PATIENT BECOMES PREGNANT WHILE TAKING THESE DRUGS,THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMA-

WARNER CHILCOTT

5

NENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN).

This adverse reaction is more common during long-term use of the drug but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED DURING TOOTH DEVELOPMENT UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in young animals (rats and rabbits) given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has been noted in animals treated early in pregnancy.

The antianabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated, and if therapy is prolonged, serum level determinations of the drug may be advisable.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This has been reported rarely with minocycline.

Central nervous system side effects including lightheadedness, dizziness, or vertigo have been reported with minocycline therapy. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and usually disappear rapidly when the drug is discontinued.

PRECAUTIONS

General

As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

Pseudotumor cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracyclines. The usual clinical manifestations are headache and blurred vision. Bulging fontanels have been associated with the use of tetracyclines in infants. While both of these conditions and related symptoms usually resolve after discontinuation of the tetracycline, the possibility for permanent sequelae exists.

Incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy when indicated.

Information for Patients

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema. This reaction has been reported rarely with use of minocycline.

Patients who experience central nervous system symptoms (see WARNINGS) should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy.

Concurrent use of tetracycline may render oral contraceptives less effective (see Drug Interactions).

Laboratory Tests

In venereal disease when coexistent syphilis is suspected, a dark-field examination should be done before treatment is started and the blood serology repeated monthly for at least four months.

In long-term therapy, periodic laboratory evaluations of organ systems, including hematopoietic, renal, and hepatic studies should be performed.

Drug Interactions

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium or magnesium, and iron-containing preparations.

The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

Concurrent use of tetracyclines may render oral contraceptives less effective.

Drug/Laboratory Test Interactions

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Concurrent use of tetracyclines may render oral contraceptives less effective.

Drug/Laboratory Test Interactions
False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Dietary administration of minocycline in long-term tumorigenicity studies in rats resulted in evidence of thyroid tumor production. Minocycline has also been found to produce thyroid hyperplasia in rats and dogs. In addition, there has been evidence of oncogenic activity in rats in studies with a related antibiotic, oxytetracycline (ie, adrenal and pituitary tumors). Likewise, although mutagenicity studies of minocycline have not been conducted, positive results in *in vitro* mammalian cell assays (ie, mouse lymphoma and Chinese hamster lung cells) have been reported for related antibiotics (tetracycline hydrochloride and oxytetracycline). Segment I (fertility and general reproduction) studies have provided evidence that minocycline impairs fertility in male rats.

Teratogenic Effects: *Pregnancy:* Pregnancy Category D (see WARNINGS).

Labor and Delivery
The effect of tetracyclines on labor and delivery is unknown.

Nursing Mothers
Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from the tetracyclines, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (see WARNINGS).

Pediatric Use: see WARNINGS.

ADVERSE REACTIONS

Due to oral minocycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines.

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, pancreatitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, and increases in liver enzymes. Rarely, hepatitis and liver failure have been reported. Rare instances of esophagitis and esophageal ulcerations have been reported in patients taking the tetracycline-class antibiotics in capsule and tablet form. Most of these patients took the medication immediately before going to bed (see DOSAGE AND ADMINISTRATION).

Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Fixed drug eruptions, including balanitis, have been rarely reported. Erythema multiforme and rarely Stevens-Johnson syndrome have been reported. Photosensitivity is discussed above (see WARNINGS). Pigmentation of the skin and mucous membranes has been reported.

Renal toxicity: Elevations in BUN have been reported and are apparently dose related (see WARNINGS).

Hypersensitivity reactions: Urticaria, angioneurotic edema, polyarthralgia, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus and rarely pulmonary infiltrates with eosinophilia have been reported. A transient lupus-like syndrome has also been reported.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

Central nervous system: Bulging fontanels in infants and benign intracranial hypertension (pseudotumor cerebri) in adults (see PRECAUTIONS—General) have been reported.

Other: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid glands. Very rare cases of abnormal thyroid function have been reported.

Tooth discoloration in pediatric patients less than 8 years of age (see WARNINGS) and also, rarely, in adults have been reported. Decreased hearing has been rarely reported in patients on minocycline hydrochloride.

OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures.

DOSAGE AND ADMINISTRATION

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF MINOCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Minocycline hydrochloride capsules may be taken with or without food.

ADULTS: The usual dosage of minocycline hydrochloride capsules is 200 mg initially followed by 100 mg every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50 mg capsules may be given initially followed by one 50 mg capsule four times daily.

FOR PEDIATRIC POPULATION ABOVE 8 YEARS OF AGE: The usual dosage of minocycline hydrochloride capsules is 4 mg/kg initially followed by 2 mg/kg every 12 hours.

Uncomplicated gonococcal infections other than urethritis and anorectal infections in men: 200 mg initially, followed by 100 mg every 12 hours for a minimum of four days, with post-therapy cultures within 2 to 3 days.

In the treatment of uncomplicated gonococcal

lowed by 100 mg every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50 mg capsules may be given initially followed by one 50 mg capsule four times daily.

FOR PEDIATRIC POPULATION ABOVE 8 YEARS OF AGE: The usual dosage of minocycline hydrochloride capsules is 4 mg/kg initially followed by 2 mg/kg every 12 hours.

Uncomplicated gonococcal infections other than urethritis and anorectal infections in men: 200 mg initially, followed by 100 mg every 12 hours for a minimum of four days, with post-therapy cultures within 2 to 3 days.

In the treatment of uncomplicated gonococcal urethritis in men, 100 mg every 12 hours for five days is recommended.

For the treatment of syphilis, the usual dosage of minocycline hydrochloride capsules should be administered over a period of 10 to 15 days. Close follow-up, including laboratory tests, is recommended.

In the treatment of meningococcal carrier state, the recommended dosage is 100 mg every 12 hours for five days.

Mycobacterium marinum infections: Although optimal doses have not been established, 100 mg every 12 hours for 6 to 8 weeks have been used successfully in a limited number of cases.

Uncomplicated nongonococcal urethral infection in adults caused by *Chlamydia trachomatis* or *Ureaplasma urealyticum:* 100 mg orally, every 12 hours for at least seven days.

Ingestion of adequate amounts of fluids along with capsule and tablet forms of drugs in the tetracycline-class is recommended to reduce the risk of esophageal irritation and ulceration.

In patients with renal impairment (see WARNINGS) the total dosage should be decreased by either reducing the recommended individual doses and/or by extending the time intervals between doses.

HOW SUPPLIED

Minocycline hydrochloride capsules USP, equivalent to 50 mg or 100 mg minocycline, are supplied as:

50 mg olive and brown, size #3, capsules imprinted WC 615:
Bottles of 100 N 0047-0615-24
Bottles of 1000 N 0047-0615-32

100 mg white and olive, size #2, capsules imprinted WC 616:
Bottles of 50 N 0047-0616-19
Bottles of 1000 N 0047-0616-32

Storage Conditions: Store at controlled room temperature 15°-30° C (59°-86° F). Protect from light.

Caution—Federal law prohibits dispensing without prescription.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Minocycline HCl has been observed to cause a dark discoloration of the thyroid in experimental animals (rats, minipigs, dogs, and monkeys). In the rat, chronic treatment with minocycline hydrochloride has resulted in goiter accompanied by elevated radioactive iodine uptake and evidence of thyroid tumor production. Minocycline hydrochloride has also been found to produce thyroid hyperplasia in rats and dogs.

REFERENCES

1. National Committee for Clinical Laboratory Standards, Approved Standard: *Performance Standards for Antimicrobial Disk Susceptibility Tests*, 3rd Edition, Vol. 4(16): M2-A3, Villanova, PA. December 1984.

2. National Committee for Clinical Laboratory Standards, Approved Standard: *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, 2nd Edition, Vol. 5(22): M7-A, Villanova, PA. December 1985.

0615G025

Revised February 1996

WARNER CHILCOTT LABS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 063066 /S011, 010, 009, 008, 007, 006

CHEMISTRY REVIEW(S)

AADA 63-066/S-006, 007
63-067/S-006, 007

NAME AND ADDRESS OF APPLICANT:
Warner Chilcott, Inc.
182 Tabor Road
Morris Plains, NJ 07950

PURPOSE OF AMENDMENT/SUPPLEMENT

S-006: To provide for elimination of the overage of active drug substance in both potencies of this drug product.

S-007: To introduce a coarse screening step for the minocycline and ...ntended to prevent accidental transfer of

S-008: Stability data to support an expiration date of 24 months for the revise formulas.

DATE(S) OF SUBMISSION(S)
Submission not dated - received 3/1/96.

PHARMACOLOGICAL CATEGORY	TRADE NAME	NONPROPRIETARY NAME
Antibacterial	N/A	Minocycline Hydrochloride

DOSAGE FORM	POTENCY	RX OR OTC
Capsules	50 mg 100 mg	Rx

SAMPLES	RELATED IND/NDA/DMF	STERILIZATION
N/A	N/A	N/A

LABELING
N/A

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
N/A

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS
N/A

PACKAGING
N/A

STABILITY
N/A

REMARKS AND CONCLUSION
The firm obtained approval for these applications with a xcess of drug substance in the formulation. They now propose to eliminate this overage (S-006). The approved formulation for 100 mg capsule (as revised in Y-003, submitted 12/3/93) and the proposed revision are presented below for comparison. The approved and proposed revisions for the 50 mg capsules are proportional.

100 mg CAPSULE:

INGREDIENTS	UNIT FORMULA PER CAPSULE:		BATCH FORMULA	
	APPROVED	PROPOSED	APPROVED	PROPOSED
Minocycline HCl				
Pregel. Starch				
Magnesium Stearate				
Target Fill Weight	270.0 mg	270.0 mg		

Notes: 1. *Equivalent to 100 mg minocycline as base per capsule pl xcess at 100% potency.*
2. *Equivalent to 100 mg minocycline as base per capsule at 100% potency.*
3. *The amount of s adjusted for the amount of minocycline hydrochloride added, the total weight required to equal mg per capsule.*

The firm discussed this proposed change with the Division of Bioequivalence in December of 1992. At that time the firm concluded from this conversation (with Dr. Dighe) that a Bio study was needed to support the removal of the excess from the formula. However, it appears from an examination of the letter in the file that, during the conversation, Dr. Dighe consulted the Orange Book and decided that since this drug product is rated AB, no study was needed. In any event the firm did do a study on the 100 mg strength and have submitted the results. Dr.

Moheb Makary discussed this with me and, after consulting Mr. Harrison, I told Dr. Makary that we normally **would not** expect a biostudy to delete an overage. He indicated that was fortunate since the study suffered from a flawed design. He stated that he would waive the study rather than review it.

The firm also introduces a step for the minocycline and ntended to prevent accidenta' (S-007). The batch size will be increased The expiration dating would remain the same at 24 months.

Information submitted in support of these submissions includes:

1. Copies of the revised Master Formulas.
2. Batch records for exhibit batches of 00 mg capsules and 0 mg capsules.
3. COA's for reference lots of each strength and COA's for each exhibit batch.
4. Comparative dissolution studies of batches made with and without the excess.
5. 3 months accelerated stability data and 24 months data at 30°C for each strength.
6. Development report demonstrating that the addition of the coarse screening step does not effect the particle size of the drug product (Attachment 2).

These supplement are approvable.

RECALLS	Reviewer	Date Completed
N/A	R.C.Adams	6/5/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 063066 /S011, 010, 009, 008, 007, 006

BIOEQUIVALENCE REVIEW(S)

JUN 27 1996

41

Minocycline HCl
50 mg and 100 mg Capsules
AADA #63-066 (50 mg)
AADA #63-067 (100 mg)
Reviewer: Moheb H. Makary
63067SDW.396

Warner Chilcott Laboratories
Morris Plains, NJ
Submission Date:
March 1, 1996

Review of a Bioequivalence Study, Dissolution Data and Waiver Request

I. Objective:

The firm submitted these two supplements to provide for a reformulation for its Minocycline HCl, 100 mg and 50 mg Capsules to remove the excess of active drug substance, Minocycline HCl, USP, and making an appropriate adjustment in the amount of to maintain the target capsule weight. The firm also plans to incorporate a increase in the maximum batch size for the 100 mg strength. The firm's 50 mg capsule product is covered by a separate AADA (63-066), which is concurrently being supplemented for these changes.

To support the removal of the from the current formula the firm has submitted a single-dose, two-way crossover bioequivalence study comparing the relative bioavailabilty of Warner Chilcott Minocycline HCl Capsules, USP, 100 mg with and without a overage of Minocycline HCl, USP, taken under fasting conditions. The firm also submitted comparative dissolution profiles for batches of both the 50 mg and 100 mg strength products, with and without the excess of Minocycline HCl, USP. The firm requested a waiver of in vivo bioequivalence study requirements for its Minocycline HCL, 50 mg Capsule.

II. Background:

Warner Chilcott Laboratories had previously conducted an acceptable in vivo bioequivalence study (a single-dose study under fasting conditions) on its Minocycline HCl Capsule, 100 mg which includes a excess of Minocycline HCl, USP. Waiver was granted for the 50 mg strength which also includes a excess of Minocycline HCl, USP. The firm has held an approved AADA #63-067 for Minocycline HCl, 100 mg Capsule and AADA #63-066 for Minocycline HCl, 50 mg Capsule since July 31, 1990.

III. In Vivo Results:

Fourteen (14) healthy male subjects (12 plus two alternates) participated and completed the study.

The plasma minocycline concentrations (ng/mL) following administration of test lot A (without overage) and reference lot B (with 5% overage) are shown in Table I. The 90% confidence

intervals (log-transformed) for $AUC_{(0-TLOQ)}$, AUC_{inf} and C_{max} are shown in Table II.
The data demonstrate that there are no statistically significant differences for minocycline between the test and reference lots for $AUC_{(0-TLOQ)}$, AUC_{inf} and C_{max}. The 90% confidence intervals for each of the above parameters are within the acceptable range of 80-125%.

IV. Dissolution Data:

The firm has submitted comparative dissolution data on its previously approved minocycline HCl 100 mg and 50 mg Capsules (with a excess of Minocycline HCl) and reformulated products (without a excess of Minocycline HCl and with adjustment in the amount of using the following dissolution conditions:

Test product:	Warner Chilcott's reformulated Minocycline HCl Capsules 100 mg, lot #977N2L 50 mg, lot #976N2L
Reference product	Warner Chilcott's previously approved Minocycline HCl Capsules 100 mg, lot #637D2L 50 mg, lot #13013L
Method:	USP 23, apparatus II (paddle) at 50 rpm.
Medium:	900 mL of water
Number of Tablets:	12
Specifications:	NLT in 45 minutes.

Dissolution testing results are shown in Table III.

V. Formulations:

Warner Chilcott's reformulated and previously approved Minocycline HCl Capsules, 100 mg and 50 mg are shown below:

	Minocycline HCl Capsules			
Component	**Reformulated**		**Previously Approved**	
	50 mg	**100 mg**	**50 mg**	**100 mg**
Minocycline HCl USP	54.0[a]	108.0[b]	56.7	113.4
Pregelatinized Starch, NF				
Magnesium Stearate				
Target Fill Weight	220.0	270.0	220.0	270.0

[a] Equivalent to 50 mg of minocycline as base per capsule at 100% potency (theoretical equivalent of minocycline HCl is 92.6%). This weight will be further adjusted upon the results of the potency test.

[b] The amount of is adjusted for the amount of minocycline HCl added. The total weight for minocycline HCl and should equal 217.8 mg per capsule.

[c] Equivalent to 100 mg of minocycline as base per capsule at 100% potency (theoretical equivalent of minocycline HCl is 92.6%). This weight will be further adjusted upon the results of the potency test.

[d] The amount of is adjusted for the amount of minocycline HCl added. The total weight for minocycline HCl and should equal 267.3 mg per capsule.

VI. Comments:

1. The bioequivalence study conducted by Warner Chilcott Laboratories on it reformulated Minocycline HCl 100 mg Capsule, lot #977N2L comparing it to the previously approved formulation containing excess Minocycline HCl (AADA #63-067, Minocycline HCl 100 mg Capsule, approval dated July 31, 1990) is acceptable. However, the firm should have conducted the bioequivalence study on its the reformulated product comparing it to the reference listed product Minocin[R] 100 mg Capsules manufactured By Lederle Laboratories instead of its previously approved product.

2. Dissolution results for the reformulated products Minocycline HCl 100 mg and 50 mg Capsules are acceptable as summarized in Table III.

3. Since the amounts 54.0 mg and 108.0 mg of Minocycline HCl for the 50 mg and 100 mg strengths are equivalent to 50 mg and 100 mg, respectively, of minocycline as base per capsule at 100% potency (theoretical equivalent of minocycline HCl is 92.6%). And based on USP 23 specifications, the Minocycline HCl Capsules should contain the equivalent of not less than 90.0% and not more than 115.0% of the labeled amount of minocycline. The request to remove the excess of active drug substance, Minocycline HCl, USP, from the firm's Minocycline HCl, 50 mg and 100 mg Capsules may be granted.

4. Adjustments the amount of for Minocycline HCl Capsules, 100 mg and 50 mg are covered under SUPAC-IR , November 1995, Level 1 Changes (i.e., acceptable dissolution testing).

VII. Recommendations:

1. The dissolution testing conducted by Warner Chilcott Laboratories on its reformulated Minocycline HCl 100 mg and 50 mg Capsules, lot #977N2L and 976N2L, respectively, is acceptable. Waivers of in vivo bioequivalence study requirements for the test products are granted. From the bioequivalence point of view, the Division of Bioequivalence deems the reformulated Minocycline HCl 100 mg and 50 mg Capsules to be bioequivalent to the firm's

previously approved Minocycline HCl 100 mg and 50 mg Capsules and for which the firm currently holds an approved AADAs.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than of the labeled amount of drug in the dosage form are dissolved in 45 minutes

The firm should be informed of the above recommendations.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE_____ Date: 6/25/96

Concur _____ Date: 6/27/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MM/6-25-96/wp 63067SDW.396
cc: AADA # 63-067 and #63-066 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Makary), Drug File, Division File.

Table III. In Vitro Dissolution Testing

Drug (Generic Name): Minocycline HCl 100 mg and 50 mg Capsules
Dose Strength: 50 mg and 100
AADA No.:63-066 and 63-067
Firm: Warner Chilcott Laboratories
Submission Date: March 1, 1996
File Name: 63067SDW.396

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle:X RPM:50
No. Units Tested: 12 Capsules
Medium: 900 mL of water
Specifications:NLT in 45 minutes
Reference Drug: Warner's previously approved Minocycline HCl 100 mg and 50 mg Capsules
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times Minutes)	Test Product Lot # 977N2L, without 5% excess of Minocycline HCl Strength(mg) 100			Reference Product Lot # 637D2L, with 5% excess of Minocycline HCl Strength(mg) 100		
	Mean %	Range	%CV	Mean %	Range	%CV
15	96		2.7	98		1.4
30	101		1.2	98		1.4
45	100		1.3	99		1.4
60	102		1.2	99		1.3

Sampling Times Minutes)	Test Product Lot # 976N2L, without 5% excess of Minocycline HCl Strength(mg) 50			Reference Product Lot # 13013L, with 5% excess of Minocycline HCl Strength(mg) 50		
	Mean %	Range	%CV	Mean %	Range	%CV
15	93		2.9	100		1.6
30	97		2.0	102		1.6
45	98		1.6	103		2.0
60	98		1.4	104		1.6

Table I

TABLE 4 A comparison of arithmetic mean (%RSD) plasma minocycline concentrations (ng/mL) following administration of test lot A (without overage) and test lot B (with 5% overage)

Time (hours)	Lot A	Lot B	Ratio A/B	Statistical Significance
0	0	0		NSD
0.5	294(82)	332(105)	0.89	NSD
1.0	1095(45)	1123(41)	0.98	NSD
2.0	1288(18)	1332(16)	0.97	NSD
3.0	1240(14)	1228(15)	1.01	NSD
4.0	1163(15)	1187(17)	0.98	NSD
6.0	934(15)	974(17)	0.96	NSD
8.0	754(12)	780(18)	0.97	NSD
12	564(16)	560(18)	1.01	NSD
16	442(15)	449(20)	0.98	NSD
24	302(24)	294(28)	1.03	NSD
36	176(25)	180(34)	0.98	NSD
48	92(31)	91(47)	1.01	NSD
60	59(36)	60(59)	0.98	NSD
72	35(65)	26(116)	1.35	NSD

Lot A: Test lot A (without overage) administered under fasting conditions.

Lot B: Test lot B (with overage) administered under fasting conditions.

Ratio Lot A/Lot B: Ratio of arithmetic means of Lot A/Lot B.

Statistical Significance: Statistical significance of the ratio comparison.

NSD: No Significant Difference ($p > 0.05$).

Table II

TABLE 7 Mean minocycline parameters and a statistical comparison of the test lot A (without overage) to the test lot B (with overage)

	$AUC_{(0\text{-}TLQC)}$	$AUC_{(0\text{-}INF)}$	C_{MAX}	T_{MAX}	$T_{1/2}$
Arithmetic Means (%RSD)					
Lot A: No overage	21392(16)	22370(17)	1412 (17)	2.07 (48)	15.2 (14)
Lot B: With overage	21530(21)	22481(22)	1417 (13)	1.79 (50)	14.4 (19)
Least Squares Means					
Lot A: No overage	21392	22370	1412	2.07	15.2
Lot B: With overage	21530	22481	1417	1.79	14.4
Ratio Lot A / Lot B	99.4%	99.5%	99.6%	116%	106%
Shortest 90% CI	95-104%	95-104%	93-106%	86-145%	97-114%
Geometric Means					
Lot A: No overage	21135	22090	1394		
Lot B: With overage	21154	22046	1406		
Ratio Lot A / Lot B	99.9%	100%	99.2%		
Shortest 90% CI	96-104%	96-104%	93-106%		
Statistical Significance for Non-Transformed Data					
Lot A *vs* Lot B	NSD	NSD	NSD	NSD	NSD
Statistical Significance for Log Transformed Data					
Lot A *vs* Lot B	NSD	NSD	NSD		

MINOCYCLINE HCl 100 MG CAPSULE

MEAN DATA (N=14 SUBJECTS)